

CONTINUING EDUCATION

EDUCATIONAL OBJECTIVES

After participating in this activity, clinicians should be better able to

- Perform diagnostic/molecular testing (EGFR, KRAS, EML4-ALK) for NSCLC according to current evidence-based guidelines
- Optimize individual therapy plans for patients based on diagnostic/molecular testing results.
- Incorporate data regarding novel therapeutic agents that can provide the most advanced treatment for patients when appropriate
- Provide appropriate care and counsel for patients and their families

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Non-small cell lung cancer: Molecular targets and emerging options for care

Daniel Morgensztern, MD

STATEMENT OF NEED/PROGRAM OVERVIEW

Despite important advances in the treatment of non-small cell lung cancer (NSCLC) over the last several years, effective treatment of advanced-stage disease remains challenging.¹ Although best practices have been outlined by the National Comprehensive Cancer Network², clinicians are often unable to utilize the preferred agent or combination of agents due to advanced disease stage, advanced patient age, poor performance status, or a potential increased risk of drug-related toxicity.² The development of screening strategies that allow for early diagnosis and comprehension of tumor biology will likely improve outcomes in these patients, as will utilization of investigational agents that are associated with positive patient response.^{2,3} Preliminary results appear promising, and researchers are hopeful that large strides will be made towards extended life in NSCLC patients over the next few years.

CE INFORMATION

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Fee information: There is no fee for this educational activity.

Media: Monograph and Web site (myCME.com)

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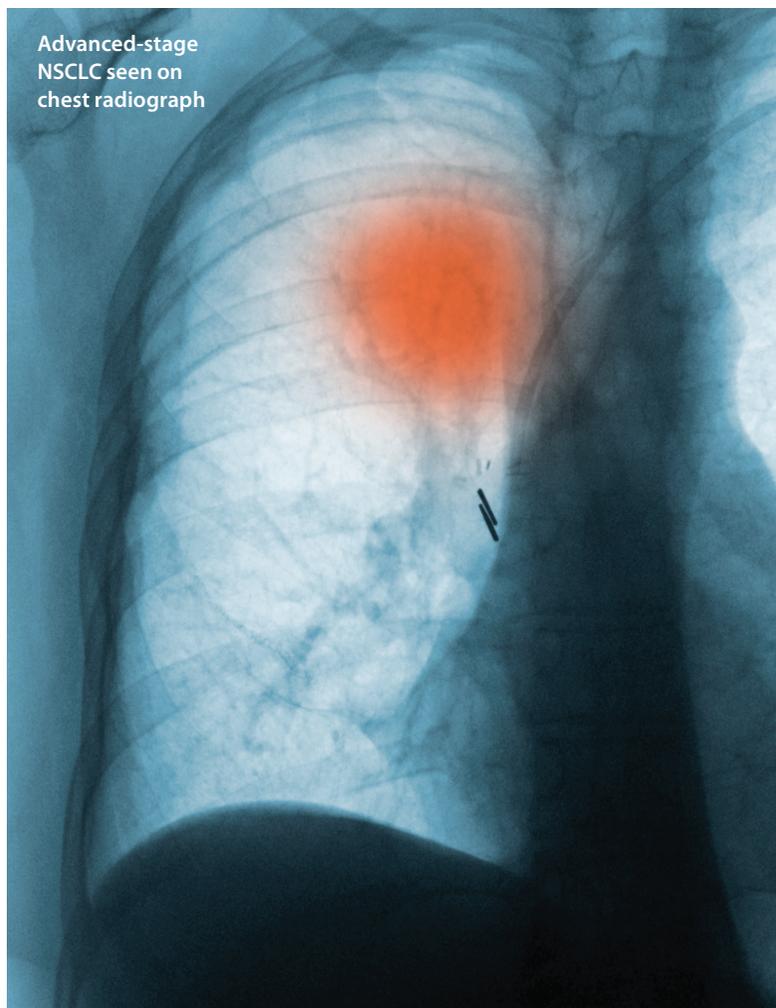
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Non-Small Cell Lung Cancer: Molecular Targets and Emerging Options for Care



Advanced-stage NSCLC seen on chest radiograph

DANIEL MORGENSZTERN, MD

Lung cancer is the leading cause of cancer-related death in the United States, with an estimated 226,160 new cases and 160,340 deaths from the disease expected in 2012.¹ Of all lung cancers, approximately 87% are classified as non-small cell lung cancer (NSCLC) and 13% as small-cell cancers.² The 5-year survival for lung cancer is approximately 15%, with the high mortality rate being largely related to advanced stage of disease at diagnosis.³

Survival in NSCLC has improved substantially over the past few decades.^{4,5} However, although chemotherapy has an established role in the treatment of advanced disease with improved survival compared to best supportive care, the benefits of the standard platinum-based doublets appear to have reached a plateau with no significant differences in survival among different platinum-based combinations.⁶ The main exception is the differential activity of pemetrexed according to histology; the combination of cisplatin plus pemetrexed was found to be more active than

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the gemcitabine doublet in patients with non-squamous histology, whereas the gemcitabine doublet was more effective in patients with squamous cell carcinoma.⁷

An increased understanding of the molecular biology of lung cancer has facilitated the development of targeted therapies. Among the new targets tested in lung cancer, three have been validated and approved for clinical use, including epidermal growth factor receptor (EGFR), vascular endothelial growth factor (VEGF), and anaplastic lymphoma kinase (ALK). This review will survey the current and emerging molecular targets under investigation in NSCLC and assess predictive biomarker testing and the individualization of therapy in this setting.

PREDICTIVE BIOMARKER TESTING AND THE INDIVIDUALIZATION OF THERAPY IN NSCLC

EGFR EGFR is a member of a family of transmembrane proteins that have an extracellular ligand binding domain, a transmembrane domain, and an intracellular tyrosine kinase. Binding of EGF to the receptor EGFR leads to activation of the intracellular tyrosine kinase domain of EGFR, which then initiates a cascade of intracellular signalling, ultimately promoting cell growth.⁸ EGFR can be targeted by monoclonal antibodies, such as cetuximab, or small-molecule EGFR tyrosine kinase inhibitors (TKIs), including gefitinib and erlotinib.

Cetuximab, a monoclonal antibody that targets EGFR, is currently approved for colorectal and head and neck cancer. In NSCLC, cetuximab demonstrated a survival advantage in the FLEX phase 3 trial of 1,124 chemotherapy-naïve patients with advanced disease.⁹ Patients were randomized to standard chemotherapy with or without cetuximab. Cetuximab plus chemotherapy provided a 1.2-month improvement in median survival compared with chemotherapy alone (11.3 months versus 10.1 months; hazard ratio [HR] = 0.87; 95% confidence interval [CI], 0.762–0.996; $P = 0.044$). In contrast, the BMS099 study showed no survival advantage for the addition of cetuximab to carboplatin plus paclitaxel in comparison to chemotherapy alone.¹⁰ A retrospective evaluation of the FLEX trial suggested that increased expression of EGFR by immunohistochemistry (H-scores above 200) may be a predictor for response of chemotherapy plus cetuximab.¹¹ The Southwest Oncology Group (SWOG) 0819 is a large study evaluating the role of cetuximab in the first-line therapy for advanced-stage NSCLC.

Gefitinib received FDA approval in May 2003 based on two phase 2 trials reporting encouraging results in previously treated patients with advanced NSCLC.^{12,13} However, the lack of survival improvement compared to best supportive care in the confirmatory phase 3 Iressa Survival Evaluation

in Lung Cancer (ISEL) trial led to the eventual discontinuation of the US approval.¹⁴ In the meantime, erlotinib was approved by the FDA for use as second- or third-line treatment of advanced NSCLC in 2004 after showing improved survival compared to best supportive care (6.7 months versus 4.7 months, $P < 0.001$) in the National Cancer Institute of Canada Clinical Trials (NCIC BR.21) trial.¹⁵ This indication was expanded in 2010 to include maintenance erlotinib, given the survival benefit observed in the SATURN (Sequential Tarceva in Unresectable NSCLC) trial.¹⁶

Certain patient characteristics are predictive of a superior response to EGFR-targeted agents, including adenocarcinoma histology, female gender, East Asian ethnicity, and never smoking. Sequence analysis of archived tumor tissues revealed mutations in the tyrosine kinase domain of *EGFR*, including in-frame deletions in exon 19 and a specific missense mutation in exon 21 (L858R).^{17–19} In the United States, approximately 15% of patients with adenocarcinoma of the lung harbor activating *EGFR* mutations, which have been associated with improved response rates and progression-

The American Society of Clinical Oncology recommends that all patients with NSCLC be tested for EGFR mutations.

free survival (PFS) compared to chemotherapy.²⁰ The Iressa Pan-Asia Study (IPASS) confirmed the role of activating *EGFR* mutations in predicting response to gefitinib.²¹ In this study, which included only patients who were never or light smokers, treatment with gefitinib was associated with a significant prolongation of PFS compared to chemotherapy with carboplatin plus paclitaxel in patients with activating *EGFR* mutations, whereas the opposite effect was observed in those with wild-type *EGFR*.²² Since then, several additional studies have confirmed the benefit from TKIs compared to chemotherapy as first-line treatment for patients with advanced NSCLC.^{23–26}

The American Society of Clinical Oncology (ASCO) recommends that all patients with NSCLC be tested for EGFR mutations.²⁰ However, evidence suggests that patients with squamous cell carcinoma are unlikely to have EGFR mutations, prompting the National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) guidelines to specify that only patients with non-squamous histology be evaluated for EGFR mutations.^{27,28}

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Despite the success of the EGFR inhibitors in patients with activating mutations, who have frequent and durable responses compared to standard chemotherapy, essentially all eventually develop tumor progression. The most common mechanism of acquired resistance to EGFR TKIs is the presence of the T790M mutation in exon 20, representing approximately 50% of cases. Other causes include *MET* amplification, *PIK3CA* mutations, and transformation to small cell histology.²⁹ Potential ways to overcome resistance include agents that bind irreversibly to EGFR or target downstream mediators of EGFR signaling; target multiple EGFR family members; and/or simultaneously inhibit EGFR, the MET pathway, and other signaling pathways. Irreversible EGFR inhibitors currently in development include dacomitinib, an inhibitor of EGFR/HER-1, HER-2, and HER-4, and afatinib (BIBW 2992), an inhibitor of EGFR/HER-1, HER-2, and HER-4.³⁰

VEGF Vascular endothelial growth factor (VEGF) is the major regulator of angiogenesis in both normal and tumor tissues.³¹ Several cancers, including NSCLC, have demonstrated increased VEGF expression. Bevacizumab, a humanized monoclonal antibody to VEGF, was approved in 2006 for the first-line treatment of patients with unresectable, locally advanced, recurrent, or metastatic non-squamous NSCLC in combination with carboplatin and paclitaxel. The approval was based on a phase 3 trial conducted by

Molecular predictors for response to chemotherapy have recently emerged, including ERCC1, RRM1, BRCA1/RAP80 and TS.

Sandler and colleagues that demonstrated a survival benefit when bevacizumab was added to paclitaxel plus carboplatin in patients with NSCLC.³² The trial was limited to patients with non-squamous cell histology because previous clinical trial data had suggested an increased incidence of fatal hemoptysis in patients with squamous cell NSCLC.³³ The median PFS was 6.2 months with bevacizumab plus chemotherapy versus 4.5 months with chemotherapy alone (HR for disease progression = 0.66; $P < 0.001$), and response rates were 35% and 15% ($P < 0.001$), respectively. In a second study, the AVAiL trial, the addition of bevacizumab to chemotherapy with cisplatin and gemcitabine prolonged PFS but not overall survival (OS).³⁴

Although several multitargeted VEGF TKIs have been tested in advanced NSCLC, none met the primary endpoint,

although toxicity was increased.³⁵ Thus, bevacizumab remains the only approved antiangiogenic agent in this setting.

ALK Crizotinib is a selective adenosine-5'-triphosphate (ATP)-competitive ALK and mesenchymal epithelial transition factor (MET)/hepatocyte growth factor (HGF) TKI that received accelerated FDA approval in August 2011 for the treatment of patients with locally advanced or metastatic NSCLC positive for ALK rearrangements through detection by a United States FDA-approved method. Such ALK rearrangements are estimated to occur in approximately 3% to 5% of NSCLC cases. Approval of crizotinib was based on the results of a phase 1/2 trial showing an overall response rate of 57% (47 of 82 patients), with an additional 33% (27 patients) achieving stable disease, mostly through minor responses below 30% reduction from baseline tumor size.³⁶ At the time of study cut-off, the median PFS had not been reached, with a 72% probability of the 6-month PFS being met. In the 2011 update, the 1-year and 2-year OS rates were 77% and 64%, respectively.³⁷ In the PROFILE 1005 study, the preliminary results with the first 439 evaluable patients showed an overall response rate (ORR) of 53% and a PFS of 8.5 months.³⁸ Although approximately half of the patients experienced visual effects, nausea, and vomiting, adverse effects were mostly mild, and the drug was very well tolerated. Phase 3 trials of first-line crizotinib versus chemotherapy (NCT01154140) as well as second-line crizotinib monotherapy (NCT00932893) for patients with ALK-positive tumors are underway.

ADVANCES IN UNDERSTANDING OF NSCLC BIOLOGY

Treatment decisions for patients with lung cancer have historically been based on tumor histology. However, the pretreatment detection of response-predictive markers could facilitate a more personalized approach to therapy whereby the most appropriate and efficacious treatment can be selected for each patient. One such approach is treatment directed at driver mutations, such as the previously reviewed mutations in EGFR and ALK.³⁹ Although such therapies are associated with high and prolonged responses, only a minority of such patients harbors the target mutations. Therefore, a new approach is needed for the vast majority of patients.

Molecular predictors for response to chemotherapy have recently emerged, including excision repair cross-complementing 1 (ERCC1), regulatory subunit of ribonucleotide reductase (RRM1), breast cancer 1 (BRCA1)/receptor-associated protein 80 (RAP80), and thymidylate synthase (TS).^{40,41}

ERCC1 The *ERCC1* gene codes for the 5' endonuclease of the nucleotide excision repair complex (NER) complex,

which repairs DNA damage, thereby mediating resistance to various chemotherapies by repairing chemotherapy-induced DNA damage. ERCC1 levels can be predictive of platinum sensitivity and provide prognostic information.^{42,43} In the International Adjuvant Lung Trial (IALT), patients were randomized to receive cisplatin-based doublet chemotherapy or observation.⁴⁴ Chemotherapy increased OS by 4%, but

The development of novel treatment options for NSCLC is increasingly based on the ability to detect driver mutations in tumor specimens.

no benefit was observed with chemotherapy in patients with ERCC1-positive tumors. However, patients with ERCC1-positive tumors had a better overall prognosis than those with ERCC1-negative tumors, with a 5-year survival rate in the observation arm of 46% versus 39% (HR = 0.66; 95% CI, 0.49–0.90; $P < 0.009$). Several trials evaluating the predictive utility of ERCC1 are currently accruing patients.

RRM1 Regulatory subunit of ribonucleotide reductase (*RRM1*) encodes an enzyme involved in DNA repair and synthesis. As with ERCC1, expression of RRM1 has been associated with prognosis in NSCLC, with longer survival reported in patients with high expression.⁴⁴ RRM1 expression is also considered to be a strong predictor of therapeutic efficacy with gemcitabine-based chemotherapy. A recent meta-analysis of 18 trials found that the response rates to gemcitabine-containing regimens were significantly higher in patients with low or negative RRM1 (odds ratio [OR] = 0.31; 95% CI, 0.21–0.45; $P < 0.00001$).⁴⁵ These patients also had a 3.94-month longer survival (95% CI, 2.15–5.73; $P < 0.0001$) and a 2.64-month longer time to progression (95% CI, 0.39–4.89; $P = 0.02$) than those with high or positive RRM1.

BRCA1/RAP80 Another predictive biomarker is *BRCA1*, a tumor suppressor gene involved in the repair of DNA double-strand breaks through homologous recombination and transcription-coupled nucleotide excision repair.^{46,47} The associated marker RAP80 is a ubiquitin-binding protein that may specifically recognize DNA damage and help target the BRCA1 complex to these sites.^{48,49} Although *BRCA1* mutations are linked to an increased risk of breast and ovarian cancer in women, BRCA1 has also emerged as a potential predictive biomarker for chemotherapy in NSCLC, with decreased expression associated with cisplatin sensitivity and increased expression predictive of improved outcomes with

taxanes and other antimicrotubulin agents.⁵⁰ In one study, 123 patients with metastatic NSCLC were selected for treatment using a customized approach based on their BRCA1 mRNA levels. Patients with low levels received cisplatin plus gemcitabine, those with intermediate levels received cisplatin plus docetaxel, and those with high levels received docetaxel alone.⁵¹ The results suggested that chemotherapy customized according to BRCA1 expression level was associated with excellent median and 2-year survival. This outcome was potentially influenced by RAP80 expression in the three BRCA1 groups; in patients with both low BRCA1 and low RAP80 levels, median survival with cisplatin plus gemcitabine treatment exceeded 26 months.

TS TS, another potential predictive marker, is a key enzyme in folate metabolism and a major target of several chemotherapy drugs, including pemetrexed. This marker is currently being evaluated as a predictive biomarker for improved outcomes with pemetrexed in patients with non-squamous cell NSCLC.^{49,52} To date, low expression of TS has been associated with improved outcomes with pemetrexed. The predictive power of TS expression will be tested prospectively in the EPIC (Elderly and Poor Performance Status Individualized Chemotherapy) trial, in which patients with previously untreated advanced NSCLC will be randomized to standard therapy or individualized therapy based on TS, ERCC1, and RRM1 mRNA levels.

Although initial studies suggest a role for molecular markers in the prediction of response to chemotherapy, their incorporation into the clinical practice will depend on the results from prospective randomized trials.

NOVEL TREATMENT OPTIONS FOR NSCLC

The development of novel treatment options for NSCLC is increasingly based on the ability to detect driver mutations in tumor specimens from patients with lung cancer and then selectively target those molecular lesions. To this end, the National Cancer Institute's Lung Cancer Mutation Consortium (LCMC) has identified driver mutations in tumors from 1,000 patients and provided the results to clinicians so that patients can receive optimized treatment or be entered into targeted therapeutic trials.⁵³ Currently, the LCMC has 14 member institutions that enroll patients with stage IIIB/IV lung cancer for tumor testing for mutations or alterations in the following 10 genes: *KRAS*, *EGFR*, *HER2*, *BRAF*, *PIK3CA*, *AKT1*, *MEK1*, *NRAS*, *ALK* (rearrangements), and *MET* (amplifications). In 2011, 830 patients had been enrolled, with an average of 50 additional patients enrolling monthly. Driver mutations were reported in 60% of patients. The prevalence of mutations detected

were as follows: *KRAS*, 25%; *EGFR*, 23%; *ALK* rearrangements, 6%; *BRAF*, 3%; *PIK3CA*, 3%; *MET* amplifications, 2%; *HER2*, 1%; *MEK1*, 0.4%; *NRAS*, 0.2%; and *AKT1*, 0%.⁵³ These findings are important to facilitate selective treatment for patients with available agents and provide a rationale for the development of therapies for multiple other targets. As a result of these recent discoveries, several investigational agents are in clinical development for the treatment of patients with NSCLC. Those in later stages of development are described below.

Dual, irreversible EGFR/HER2 tyrosine kinase inhibitors

As previously noted, an important consideration with currently available EGFR inhibitors is the development of resistance. This issue may be overcome with the use of second-generation irreversible EGFR inhibitors. One example of a novel irreversible EGFR inhibitor is afatinib (BIBW 2992), which inhibits EGFR/HER1, HER2, and HER4 and is currently in phase 3 trials for patients with lung cancer. Results of a phase 2b/3 study (LUX-Lung 1) of afatinib plus usual care versus placebo plus usual care in patients who progressed after one to two lines of chemotherapy and at least 12 weeks of erlotinib or gefitinib were recently reported.⁵⁴ The study randomized 585 patients to receive treatment with afatinib ($n = 390$) or placebo ($n = 195$). While no significant OS benefit was observed with afatinib, median PFS was longer in the afatinib group (3.3 months; 95% CI, 2.79–4.40) compared with the placebo group (1.1 months; 0.95–1.68; HR = 0.38; 95% CI, 0.31–0.48; $P < 0.0001$). In addition, 7% of patients had a partial response versus one patient in the placebo group. As with other agents in this class, common side effects were diarrhea (87%) and rash or acne (78%). In the first-line setting for patients with activating EGFR mutations, the LUX-Lung 3 trial, showed a significant improvement in response rate (56% versus 23%; $P < 0.0001$) and prolongation of PFS (11.1 versus 6.9 months; HR 0.58, 95% CI 0.43–0.78; $P = 0.0004$) for afatinib compared to pemetrexed plus cisplatin.⁵⁵ Preliminary results of an ongoing trial evaluating the combination of afatinib and cetuximab for patients with EGFR mutant NSCLC progressing through first-line erlotinib in 45 patients showed a response rate (RR) of 51% and a disease control rate (DCR) of 93%, generating great interest in the use of irreversible EGFR inhibitors.⁵⁶

Dacomitinib, an irreversible inhibitor of EGFR/HER1, HER2, and HER4, is also under evaluation in lung cancer. A phase 3 trial of dacomitinib as monotherapy after progression during standard chemotherapy is underway (BR26; NCT01000025), and a randomized, double-blinded phase 3 clinical trial (ARCHER; NCT01360554) is comparing

the efficacy of dacomitinib versus erlotinib in patients with advanced NSCLC with or without mutated *KRAS*.

Immunotherapy Although immunotherapy in lung cancer has been associated with disappointing results, recent studies targeting programmed death 1 (PD-1) have been encouraging. The PD-1 protein is a T-cell co-inhibitory receptor, and one of its ligands, PD-L1, plays a central role in tumor evasion of the host immune system. A blockade of interactions between PD-1 and PD-L1 enhances immune function in vitro and mediates antitumor activity in preclinical models. In a phase 1 study of the anti-PD1 antibody BMS 936558, 76 patients with NSCLC were accrued, with a RR of 18% and PFS of 26% at 24 weeks.⁵⁷ Response rates were observed in all dose levels and were higher in squamous histology compared to non-squamous (33% versus 12%). Of note, responses were not observed among patients with PD-L1-negative tumors. In a second simultaneously presented phase 1 study, 75 patients with NSCLC were treated with the anti-PD-L1 antibody.⁵⁸ At 24 weeks, the RR was 10% and the PFS was 31%, showing that both PD1 and PD-L1 are valid and promising targets.

CONCLUSIONS

In the last few years, important advances have contributed to the understanding of the molecular pathogenesis of lung cancer and facilitated the discovery of new therapeutic targets and drugs. Recent studies have shown significant benefit from the use of personalized therapy, where the appropriate drug is administered in patients who have a specific predictor for response. Furthermore, preliminary studies indicate an expanding role of immunotherapy in patients with NSCLC, with durable responses observed after the use of antibodies targeting the PD1-PDL1 pathway. Because only a small percentage of patients achieve benefit from each specific therapy, it remains important to continue the search for predictors for response in an attempt to maximize the therapeutic benefits and decrease the unnecessary risk of toxicity in those with a low probability of response. ■

Dr. Morgensztern is Assistant Professor, Division of Oncology, Yale University School of Medicine, New Haven, Connecticut

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