Biomarkers with Predictive and Prognostic Function in Non–Small Cell Lung Cancer: Ready for Prime Time?

Charu Aggarwal, MD, MPH; Neeta Somaiah, MD; and George R. Simon, MD, Philadelphia, Pennsylvania

Key Words
Prognostic marker, predictive marker, lung cancer

Abstract
Lung cancer is the leading cause of cancer-related mortality in the United States. Non–small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancers. Most patients with NSCLC present with locoregionally advanced or metastatic disease, for which response rates and median overall survival remain poor. Platinum-based chemotherapy is the mainstay of treatment for NSCLC in both adjuvant and metastatic disease. Personalized chemotherapy and targeted biologic therapy based on a tumor’s histologic and molecular profile have already shown promise in optimizing efficacy. Various markers are currently being investigated for their ability to guide treatment decision-making and management. This article describes these predictive and prognostic markers and details their current role, benefit, and potential future use in the management of patients with NSCLC. (JNCCN 2010;8:822–832)

Lung cancer is the leading cause of cancer-related mortality in the United States.1 Non–small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancer cases and predominantly encompasses the adenocarcinoma, squamous cell carcinoma, and large cell carcinoma histologies. Early-stage NSCLC represents a minority of cases and is often curable with surgery with or without adjuvant chemotherapy. Radiation therapy, surgery, and chemotherapy have been used alone or in combination to maximize therapeutic benefit in the locally advanced setting. Most patients with NSCLC, however, present with distant metastases, for which chemotherapy is the mainstay of treatment. Targeted therapies are increasingly being used with encouraging results not only in patients with specific molecular features but also in the broader population of patients with NSCLC.2–4 Despite these advances in treatment, overall prognosis remains poor in patients with advanced disease. Personalizing therapy based on an individual patient’s molecular profile is a potentially promising approach to optimizing efficacy with the available agents. Molecular determinants that guide treatment decision-making are described in this article. These determinants may have a prognostic or predictive function and are commonly referred to as prognostic or predictive markers, respectively. Each of these attributes of a molecular determinant can be exploited for therapeutic gain.

A prognostic determinant or marker refers to a tumor characteristic that is useful for estimating patient’s outcome independent of therapeutic decisions (i.e., survival is different for marker-positive vs. -negative status). Predictive markers are useful in making therapeutic decisions (i.e., the effect of treatment is different depending on marker-positive vs. -negative status). However, some markers, such as excision repair cross-complementation group 1 (ERCC1) and ribonucleotide reductase M subunit 1 (RRM1; vide infra), have both prognostic and predictive functions. In the adjuvant setting, the prognostic and predictive functions of molecular determinants are being used to guide treatment
in ongoing trials. In the advanced setting, the predictive function of molecular determinants is more useful for guiding treatment decisions. This article focuses on the current clinical use of prognostic and predictive markers in deciding treatment for patients with NSCLC.

**ERCC1**

Cisplatin-based adjuvant treatment is the standard of care in patients with completely resected stage II and III NSCLC.5-10 Adjuvant chemotherapy in this setting is associated with improvement in survival.8 Cisplatin inhibits replication by binding to DNA and forming platinum–DNA adducts, causing strand breaks when the DNA helices unwind in preparation for replication. The nuclear excision repair (NER) family of genes is involved in repair of these DNA strand breaks.11 The ERCC1 enzyme is one of the proteins involved in the final step of the NER pathway that recognizes and removes cisplatin-induced DNA adducts. ERCC1 is also important in the repair of interstrand crosslinks in DNA and in recombination processes. Removal of platinum–DNA adducts by the proteins of the NER pathway reverses the tumoral DNA damage induced by cisplatin, thereby leading to cisplatin resistance. High tumoral ERCC1 expression, therefore, predicts for cisplatin resistance and serves as a predictive molecular determinant for this chemotherapeutic agent.

The primary, nature-intended, function of ERCC1 is to repair DNA damage caused by exposure to natural mutagenic elements, such as ionizing radiation and DNA damaging agents. An intact DNA repair mechanism, as reflected by high nuclear ERCC1 expression, therefore preserves genomic integrity. High tumoral levels of ERCC1 have therefore been associated with better outcomes in patients with early-stage disease who underwent curative resection, presumably because of more indolent tumor behavior secondary to a tumoral genome that has less DNA damage and therefore more closely resembles the genome of a normal cell. In this context, ERCC1 functions as a prognostic marker.

The prognostic function of ERCC1 was first observed in a retrospective analysis of patients with NSCLC who underwent curative resection. ERCC1 was measured using reverse transcriptase polymerase chain reaction (RT-PCR) and its expression was normalized using 18SrRNA expression; therefore its levels were expressed as a unit-less ratio. Using an ERCC1 value of 50 to dichotomize the cohort, a statistically significant difference in median survival was seen for patients with ERCC1 expression greater than 50 (94.6 vs. 35.5 months; \( P = .01 \)). Multivariate analysis showed that high ERCC1 expression independently predicted for longer survival. No statistically significant correlations were seen in ERCC1 expression between tumor tissue and normal lung, highlighting the need to measure tumoral ERCC1 for clinical purposes.12

The predictive effect of ERCC1 was assessed in a retrospective study of 56 patients with advanced NSCLC treated with cisplatin and gemcitabine.13 Median overall survival was significantly longer in patients with low ERCC1 (61.6 weeks) compared with those with high ERCC1 (20.4 weeks).

Olaussen et al.14 assessed patient samples from the International Adjuvant Lung Trial (IALT) to define biomarkers predictive for chemotherapy response and resistance in the adjuvant setting for NSCLC. In the IALT study, patients with curatively resected NSCLC were randomized to adjuvant chemotherapy (chemotherapy group) or no chemotherapy (control group). In the overall study population, adjuvant chemotherapy improved 5-year survival by 4.1% \( (P < .03) \). Immunohistochemistry was used to analyze tumor samples for ERCC1 in addition to other markers. Among patients with ERCC1-negative tumors, the 5-year overall survival rate was significantly longer for those in the chemotherapy group versus the control group (47% vs. 39%, respectively). Disease-free survival among patients with ERCC1-negative tumors was also longer in the chemotherapy group than in the control group. Among patients with ERCC1-positive tumors, no difference in overall survival was seen between the adjuvant chemotherapy and control groups. Additionally, among patients in the control group, those with ERCC1-positive tumors experienced better results than those with ERCC1-negative tumors (adjusted hazard ratio for death, 0.66; 95% CI, 0.49–0.90; \( P = .009 \)), further highlighting the prognostic significance of ERCC1. These results suggest that determining ERCC1 expression in completely resected NSCLC can help select patients likely to benefit from additional platinum-based adjuvant chemotherapy.
RRM1

RRM1 is the regulatory component of ribonucleotide reductase and is a critical component of DNA synthesis and repair.15 It is also the main target of the cytotoxic agent gemcitabine, and therefore levels inversely correlate with therapeutic benefit from gemcitabine.16–18 Hence, RRM1 has a predictive function as far as gemcitabine is concerned.

RRM1 has also been associated with differential survival outcomes in patients with NSCLC.19 Increased RRM1 predicts for decreased tumor invasiveness and metastatic potential, therefore predicting for more indolent behavior, perhaps mediated through its direct correlation with phosphatase and tensin homolog (PTEN) protein expression.20 High RRM1 levels therefore have a prognostic function.

Zheng et al.21 measured RNA expression of RRM1 and ERCC1 using RT-PCR on fresh frozen and formalin fixed paraffin-embedded tumor samples. This study showed that RRM1 expression correlated with expression of ERCC1 and that patients whose tumors had high expression of RRM1 had superior survival compared with the low expression group (disease free survival, > 120 vs. 54.5 months; HR, 0.46; P = .004, and overall survival, > 120 vs. 60.2 months; HR, 0.61; P = .02). In a subgroup analysis, the survival advantage was higher in patients with high expression of both RRM1 and ERCC1. This study showed that coexpression of 2 different proteins characterized a subpopulation of patients with NSCLC with superior prognosis.21

In a similar study, Rosell et al.22 analyzed samples for ERCC1 and RRM1 from 100 patients with advanced-stage NSCLC undergoing chemotherapy with gemcitabine/cisplatin, gemcitabine/cisplatin/vinorelbine, or gemcitabine/vinorelbine followed by vinorelbine/ifosfamide. ERCC1 and RRM1 mRNA expression was determined by RT-PCR in paraffin-embedded samples obtained from bronchoscopy, showing a strong correlation between the expression levels (P < .001). In the gemcitabine/cisplatin arm, patients with low RRM1 mRNA expression levels had significantly longer median survival than those with high levels (13.7 vs. 3.6 months; P = .009), owing to the increased response of gemcitabine chemotherapy as predicted by low RRM1. Among all patients treated with chemotherapy, median survival was significantly longer among those with low expression of RRM1 and ERCC1 than among those with high levels of both genes (P = .016).

Based on these findings, a prospective, phase II trial of combination chemotherapy was designed for treating metastatic NSCLC based on expression of ERCC1 and RRM1, with the primary intent of determining feasibility. Patients with low ERCC1 received carboplatin and those with low RRM1 received gemcitabine. Based on this, patients were allocated into 1 of 4 treatment groups: low RRM1/low ERCC1 (gemcitabine and carboplatin), low RRM1/high ERCC1 (gemcitabine and docetaxel), high RRM1/low ERCC1 (docetaxel and carboplatin), and high RRM1/high ERCC1 (docetaxel and vinorelbine). An observed response rate of 44% with an overall survival of 13.3 months and progression-free survival of 6.6 months appeared promising.23 Encouraged by these results, a prospective randomized phase III trial, commonly referred to as the MADE-IT (Molecular Analyses Directed Individualized Therapy) trial, is underway to compare the same personalized chemotherapy approach to a standard doublet of carboplatin and gemcitabine.24

BRCA1

BRCA1 is a protein that belongs to the mismatch repair pathway, a mechanism of DNA repair distinct from NER, and functions as a differential regulator of chemotherapy-induced apoptosis.25 BRCA1 functions as a sensitizer to apoptosis induced by antimicrotubulin agents, such as taxanes and vinca alkaloids, and also abrogates the apoptosis induced by a range of DNA-damaging agents, including cisplatin and etoposide.26 Low expression of BRCA1 mRNA closely correlates with ERCC1 mRNA expression and predicts a more favorable outcome in patients with locally advanced NSCLC treated with cisplatin/gemcitabine, followed by surgery.27

The phase III Spanish Customized Adjuvant Treatment (SCAT) trial is based on data showing that low BRCA1 mRNA levels predict for longer survival with cisplatin-based chemotherapy, whereas high BRCA1 levels predict for resistance to cisplatin and therefore should be treated with a taxane-based regimen instead.28,29 In a recently reported feasibility study, adjuvant chemotherapy was customized based on BRCA1 mRNA levels in 84 patients with completely resected NSCLC.30 Patients received docetaxel for high levels of BRCA1, docetaxel/cispl-
mous cell carcinomas suggest that pemetrexed may be a more effective drug for nonsquamous NSCLCs. A retrospective analysis of a prospective randomized phase III study comparing pemetrexed with docetaxel in patients with non-squamous carcinomas showed that those treated with pemetrexed had improved overall survival (9.3 vs. 8.0 months). Conversely, docetaxel appeared to yield better overall survival in patients with squamous carcinoma (7.4 vs. 6.2 months). These results seem to corroborate the treatment-by-histology interaction hypothesis generated by preclinical studies.

This histology interaction became clearly evident in a phase III trial comparing cisplatin and gemcitabine (CiG; n = 863) with cisplatin and pemetrexed (CiPe; n = 862) in patients with advanced NSCLC. This was a noninferiority, phase III, randomized study comparing overall survival between the treatment arms (HR, < 1.176); overall survival for the pemetrexed arm was noninferior to the gemcitabine arm (median survival, 10.3 vs. 10.3 months, respectively; HR, 0.94; 95% CI, 0.84–1.05). In a prespecified subset analyses, overall survival was statistically superior for the pemetrexed arm versus the gemcitabine arm in patients with adenocarcinoma (n = 847; 12.6 vs. 10.9 months, respectively) and large-cell carcinoma histology (n = 153; 10.4 vs. 6.7 months, respectively). In patients with squamous cell histology, however, a significant improvement in survival was seen among those in the gemcitabine arm versus the pemetrexed arm (n = 473; 10.8 vs. 9.4 months, respectively).

**KRAS**

The Kirsten-rous avian sarcoma (KRAS) protein is a member of the RAS family of proteins that encode small GTPases involved in cellular signal transduction. Activation of Ras signalling causes cell growth, differentiation, and survival.

In NSCLC cells, mutations in the KRAS gene usually involve codons 12 (in 90% of patients) and 13. They are mostly smoking-related and predominantly occur in adenocarcinomas. Several studies have reported that these are virtually mutually exclusive of mutations in the epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor 2 (HER2)/neu kinase domains.

Slebos et al. evaluated the relationship among
KRAS activation, tumor characteristics, and survival in patients with NSCLC. Tumors positive for KRAS mutations were smaller and less differentiated. Of 19 patients with KRAS mutation, 12 died during the follow-up period, compared with 16 of 50 patients with no mutation (\(P = .002\)). This difference in prognosis was also reflected in the duration of disease-free survival (\(P = .038\)) and the number of deaths caused by cancer (\(P < .001\)).

The association between KRAS mutations and chemotherapy, particularly adjuvant chemotherapy, was investigated in a National Cancer Institute of Canada report of a preplanned KRAS mutational analysis from a prospective trial randomizing patients with resected stage IB to II NSCLC to undergo either adjuvant cisplatin/vinorelbine or observation. In the whole population, patients who underwent chemotherapy had improved overall survival, with an HR of 0.70 (\(P = .03\)). Among 450 tumors (available for 94\% of patients enrolled), 117 had KRAS mutations. In patients with KRAS wild-type mutations, the HR for treatment with cisplatin and vinorelbine remained significant (HR, 0.69; \(P = .03\)). However, among patients whose tumors had KRAS mutations, no difference was seen in overall survival between the observation and chemotherapy groups (HR, 0.95; \(P = .87\)). KRAS mutation was not a significant prognostic marker for survival in univariate or multivariate analyses. Taken together, these prospectively collected data suggest no prognostic significance for KRAS mutations in this cohort of patients with early-stage NSCLC, and that chemotherapy with cisplatin and vinorelbine is unlikely to benefit patients whose tumors have KRAS mutations.\(^4\)

However, despite these data, and without prospective validation, KRAS mutational status should not be used to deny patients adjuvant chemotherapy.

KRAS mutations were thought to be frequently associated with resistance to EGFR inhibitors and chemotherapy.\(^{36,45}\) An analyses of samples from patients enrolled in the TRIBUTE study, a phase III trial of combination chemotherapy and erlotinib as first-line treatment in patients with advanced NSCLC,\(^{45,46}\) showed that KRAS mutations were found in approximately 21\% of tumors, and were associated with significantly decreased time to progression and overall survival in patients treated with erlotinib plus chemotherapy.\(^45\) A poorer outcome was also noted for patients with KRAS mutation treated with erlotinib in the BR.21 study, a randomized phase III study that showed activity for erlotinib versus placebo in the second- or third-line treatment of patients with advanced NSCLC.\(^4\) In a post hoc subset analysis of the BR.21 trial, 30 patients (15\%) had KRAS mutations. Response rates were 10\% for tumors with wild-type KRAS and 5\% for tumors with mutant KRAS (\(P = .69\)). Compared with placebo, significant survival benefit was associated with erlotinib in patients with wild-type KRAS but not those with mutant KRAS.\(^47\) However, these observations could be attributed to the fact that KRAS and EGFR mutations are mutually exclusive, and therefore the cohort of patients with KRAS wild-type tumors will have a subset with EGFR mutations. EGFR mutations are intricately linked to sensitivity to erlotinib or gefitinib, and therefore KRAS-mutated tumors may be perceived to predict for erlotinib resistance. To truly understand the independent effect of KRAS mutations as a predictor of erlotinib or gefitinib resistance, a cohort of patients with KRAS-mutated tumors must be compared with a cohort of patients who are wild-type for both KRAS and EGFR. Because response rates for EGFR–tyrosine kinase inhibitors (TKIs) are so low in patients with EGFR wild-type mutations, progression-free and overall survivals would have to be the appropriate end points to discern these differences.

The association of KRAS mutations and response to cetuximab seems to be less clear in NSCLC and contrary to the experience in colon cancer. Tumor samples from the FLEX study, a study that compared the triplet combination of cisplatin/vinorelbine/cetuximab with a standard doublet combination of cisplatin and vinorelbine, were analyzed for KRAS mutations. Among the 1125 patients enrolled in the FLEX trial, 19\% (\(n = 75\)) of the 395 patient samples available for KRAS mutation testing were positive.\(^2\) No differences were seen in overall or progression-free survival in patients with (\(n = 38\)) or without (\(n = 161\)) KRAS mutations who received cetuximab. Patients treated with cetuximab who developed early acne-like rash of any grade had a longer median overall survival than those without acne-like rash (\(P < .001\)).\(^48\) Therefore, the presence of rash seems to be the best predictor of clinical benefit for patients treated with cetuximab.

In a similarly designed BMS-099 trial that compared carboplatin/paclitaxel/cetuximab with carboplatin/paclitaxel, a statistically significant survival
benefit for the addition of cetuximab to carboplatin/paclitaxel could not be shown. Among the 676 patients enrolled in this trial, 17% (N = 35) of the 167 patient samples available for KRAS mutation testing were positive. Subset analyses of the KRAS mutation subgroup yielded similar results to those from the FLEX trial. Treatment-specific analyses showed no statistically significant associations between KRAS mutation status and survival. However, these were post hoc analyses and included small sample sizes, as denoted by the small numbers in the KRAS mutant category. Therefore, further studies are required before firm conclusions can be made.

**EGFR**

The EGFR is one of a family of receptors that has growth-promoting effects in NSCLC. EGFR is overexpressed in approximately 40% to 80% of NSCLC. Downstream signaling by the activated EGFR can be abrogated by small molecule inhibitors, such as erlotinib and gefitinib, or by monoclonal antibodies directed toward the extracellular domain of EGFR, such as cetuximab. Potential markers evaluated for response to these targeted agents include EGFR expression, assessed using immunohistochemistry; EGFR amplification, assessed using fluorescence in situ hybridization (FISH); and EGFR mutations.

**EGFR Mutations**

Mutations in the tyrosine kinase domain of the EGFR receptor were first discovered and reported in 2004. They are more prevalent in patients with adenocarcinoma who never smoked. In-frame deletions in exon 19 and the L858R point mutation in exon 21 are the 2 most commonly seen activating mutations in the ATP-binding pocket of the EGFR tyrosine kinase domain. The probability of response to an EGFR-TKI strongly correlates with the EGFR mutation status. A seminal phase III trial randomized previously untreated, never, or light smokers from East Asia with advanced lung adenocarcinoma to receive gefitinib (250 mg/d; n = 609) or carboplatin-paclitaxel (n = 608), of whom 261 patients were positive for the EGFR mutations. The objective response rate was 71.2% for gefitinib versus 47.3% for carboplatin/paclitaxel in the mutation-positive subgroup (P < .001) and 1.1% (1 patient) versus 23.5%, respectively, in the mutation-negative subgroup (P = .001). In patients with EGFR mutations, progression-free survival was significantly longer among those who received gefitinib than those who received carboplatin-paclitaxel (HR for progression or death, 0.48; 95% CI, 0.36–0.64; P < .001), whereas in the subgroup of 176 patients who were negative for the mutation, progression-free survival was significantly longer among those who received carboplatin-paclitaxel (HR for progression or death with gefitinib, 2.85; 95% CI, 2.05–3.98; P < .001).

In a trial conducted in Europe, treatment with erlotinib yielded a similar response rate of 70.6% in patients who were EGFR mutation–positive. The therapeutic implications of these data are that treatment with an EGFR-TKI is appropriate, especially as first-line treatment if the patient’s tumors are EGFR mutation–positive. If the mutation status is unknown or negative, chemotherapy with or without bevacizumab would be more appropriate.

EGFR mutations significantly predict for both an increased response to tyrosine kinase therapy and a favorable prognosis in patients with advanced lung adenocarcinoma, thereby making them one of the most clinically validated prognostic and predictive markers in NSCLC.

Despite the dramatic responses to TKIs, most, if not all, patients will ultimately develop resistance to these agents. Several mechanisms of resistance have been described, including the emergence of resistance mutations known as the T790M mutation. Kobayashi et al. described the presence of a second point mutation, resulting in a threonine-to-methionine amino acid change at position 790 of the EGFR tyrosine kinase domain that leads to biochemical and structural alteration that causes resistance to TKI therapy. Presence of this and other mutations seen on exon 20 of the EGFR tyrosine kinase domain predict for nonresponse to TKI therapy.

**EGFR FISH**

The recent discovery of the strong association between EGFR-TKI therapy and EGFR mutations has helped clarify the role of FISH as a predictor of response to TKIs. Two similarly designed studies comparing EGFR-TKI therapy with placebo—BR.21 (erlotinib vs. placebo) and ISEL (gefitinib vs. placebo)—showed an improved outcome with erlotinib and gefitinib, respectively, in patients with high EGFR gene copy. The perceived ability of EGFR FISH to predict response to EGFR-TKI may
be secondary to the fact that significant overlap exists between FISH positivity and presence of EGFR mutations. In the IPASS trial, patients who were FISH-positive but mutation-negative derived little or no benefit from gefitinib (essentially behaving like patients who were mutation-negative) in contrast to patients who were FISH- and mutation-positive, suggesting that EGFR mutation status is the primary determinant of response to gefitinib or erlotinib. The profile identified patients who had improved outcomes after EGFR-TKI treatment in both validation cohorts. The authors concluded that the profile could classify patients with NSCLC into good or poor outcomes after treatment with EGFR-TKIs, and may be useful in selecting patients for treatment. The current usefulness of this approach remains to be defined given that EGFR mutations are a very strong predictor response. However, the potential advantages of this approach are that the tissue is not required and that this test can be performed in serum and could potentially identify a EGFR mutation–negative cohort of patients who may derive clinical benefit from EGFR-TKIs.

**EML4-ALK**

EML4-ALK is a fusion protein in which the N-terminal half of echinoderm microtubule–associated protein–like 4 (EML4) is fused to the intracellular kinase domain of ALK and leads to expression of a chimeric tyrosine kinase with potent oncogenic activity both in vivo and in vitro.

In a retrospective genetic screen of 141 NSCLC tumors, patients with EML4-ALK translocations were significantly younger, male, and never/light smokers; were overwhelmingly adenocarcinomas, particularly of the mucinous or acinar types; and did not harbor either EGFR or KRAS mutations. EML4-ALK positivity was associated with resistance to EGFR-TKIs. A few selective ALK kinase inhibitors are in preclinical and early clinical testing, and one of them, PF-02341066 (crizotinib), showed encouraging preliminary results in EML4-ALK–positive previously treated NSCLC patients. In 50 patients with NSCLC carrying the EML4-ALK translocation, objective responses of 64% (32/50 patients; 95% CI, 49%–77%) were noted, with a disease control rate of 90% (45/50 patients; 95% CI, 78%–97%). Median duration of treatment at the time of the report was 25.5+ weeks. Mature progression-free survival data were not available. Ongoing phase III studies are comparing PF-02341066 with standard second-line chemotherapy in previously treated patients with

### Serum Proteomic Profiles as Predictors of EGFR-TKI Response

Matrix-assisted laser desorption/ionization mass spectrometry (MALDI-MS) analysis has also been used to identify patients with NSCLC who are likely to benefit from treatment with EGFR-TKIs. The MALDI-MS profile was developed from a training set of 139 patients from 3 cohorts. The profile was tested in 2 independent validation cohorts of 67 and 96 patients treated with gefitinib and erlotinib, respectively, and in 3 control cohorts of patients who were not treated with EGFR-TKIs. The profile identified patients who had improved outcomes after EGFR-TKI treatment in both validation cohorts. The authors concluded that the profile could classify patients with NSCLC into good or poor outcomes after treatment with EGFR-TKIs, and may be useful in selecting patients for treatment. The current usefulness of this approach remains to be defined given that EGFR mutations are a very strong predictor response. However, the potential advantages of this approach are that the tissue is not required and that this test can be performed in serum and could potentially identify a EGFR mutation–negative cohort of patients who may derive clinical benefit from EGFR-TKIs.
advanced NSCLC and EML4-ALK translocation. These provocative and exciting results again define a distinct subset of patients with NSCLC who have similar clinical characteristics and might benefit from selective inhibition of a target.

**Gene Expression Profiling**

Oligonucleotide array–based gene expression patterns have been studied to evaluate and develop the use of the gene expression profiles as a means to stratify risk and treatment.\(^1\) Although gene expression microarray can analyze thousands of genes at a time, it necessitates specialized techniques and complex statistics that may act as barriers to its wide application in community cancer centres. Recent reports have shown that data generated from microarrays could have both a prognostic and predictive function.

In a study by Potti et al.,\(^2\) a gene profile was developed from a cohort of 89 patients with early-stage NSCLC and validated independently in 2 groups of 25 patients from the American College of Surgeons Oncology Group (ACOSOG) Z0030 study and 84 patients from the CALGB 9761 study. The authors concluded that their expression profile was prognostic of recurrence for individual patients, with accuracies of 72% and 79%, respectively, and was a better prognostic marker of 5-year survival than clinical or pathologic stage. Therefore, this microarray profile, referred to as the metagene model, may help identify patients at high risk for recurrence and therefore more likely to benefit from adjuvant chemotherapy. A phase III trial (CALGB 30506) is currently underway in patients with stage IA disease. Patients predicted to be at a low risk will undergo observation, and those predicted to be at high risk will be randomized to chemotherapy versus observation.

Chen et al.\(^3\) developed a 5-gene signature that is closely associated with survival for patients with NSCLC. Using oligonucleotide microarray data and risk scores, 16 genes were identified that correlated with survival. Of these, 5 genes (DUSP6, MMD, STAT1, ERBB3, and LCK) were selected for RT-PCR and decision tree analysis, and were found to be independent predictors of progression-free and overall survival. This 5-gene profile helped separate patients into high-risk (n = 59) and low-risk (n = 42) groups. Patients with a high-risk gene signature had a shorter median overall survival than those with a low-risk signature (20 vs. 40 months; \(P < .001\)). Median progression-free survival in the high-risk group was 13 months compared with 29 months in the low-risk group (\(P = .002\)).

Potti et al.\(^2\) also showed that gene profiles could be used to predict chemotherapy sensitivity. Using in vitro drug sensitivity and oligonucleotide expression data, the investigators developed gene signatures that could predict for sensitivity to individual chemotherapeutic agents. They also developed a gene expression–based predictor, consisting of 50 genes that classified cell lines based on docetaxel sensitivity. The docetaxel signature predicted sensitivity with an accuracy of 80% in an independent dataset (\(P < .001\)). The study also integrated chemotherapy response signatures with oncogenic pathway deregulation to obtain information on potential drug efficacy in the context of specific pathways involved in tumorigenesis. Oligonucleotide expression array data from 17 NSCLC cell lines predicted to be resistant to docetaxel also indicated profiles suggestive of phosphotyrosine-3 kinase (PI3K) pathway activation. Cell lines with a PI3K activation profile responded to PI3K inhibitors, suggesting that cells resistant to docetaxel may be sensitive to PI3K inhibition and that PI3K inhibitors could increase docetaxel sensitivity. This work is currently being validated in prospective phase III trials.\(^4\)

**Conclusions**

The current era is marked by personalized chemotherapy, and treatment choices based on molecular determinants will be increasingly explored in the future. Barriers to the wide application of this approach include the availability of adequate tumor tissue. The hope is that increased awareness of these approaches will lead to improved initial tumor sampling that will decrease the need for repeat biopsies. Significant advances have been made in the past few years and the use of molecular markers is increasingly being incorporated in the management of patients with NSCLC.

**References**


Prognostic and Predictive Markers in NSCLC


63. Fukuoka M, Wu YL, Thongprasert S. Biomarker analyses from a phase III, randomized, open-label, first-line study of gefitinib (G) versus carboplatin/paclitaxel (C/P) in clinically selected patients (pts) with advanced non-small cell lung cancer (NSCLC) in Asia (IPASS) [abstract]. J Clin Oncol J Clin Oncol 2009;27(Suppl 1):Abstract 8006.


