Summary of Presentations from the 46th Annual Meeting of the American Society of Clinical Oncology (2010) Focus on Tumor Biology and Biomarkers Related to Lung Cancer

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Abstract: Globally, lung cancer remains the most common cause of cancer-related death. In recent years, it has become clear that development of rational molecular targeted therapies is critical to improve the outcomes of patients with lung cancer. A better understanding of the tumor biology is crucial to achieve this goal. Several new findings in the field of tumor biology were presented at the 46th Annual Meeting of the American Society of Clinical Oncology. Novel genetic mutations were identified in pleural mesothelioma using array-based technologies. Several studies on the development and testing of new molecular diagnostic tests to detect epidermal growth factor receptor tyrosine kinase mutations and *EML4-ALK* (Echinoderm Microtubule-associated Protein like 4 Anaplastic Lymphoma Receptor Tyrosine Kinase) fusion gene were presented as well.

Key Words: Lung cancer, NSCLC, Tumor biology, *EML4-ALK*, *EGFR*, Gene expression, *K-ras*, Mesothelioma.

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Lung cancer is the most common cause of cancer-related death in the United States.[1] More than half of these patients present with advanced stage disease and systemic therapy offer only modest benefits. The development of rationally developed targeted therapies is likely to improve the outcomes of patients with lung cancer significantly. Comprehensive understanding of the molecular aberrations in lung cancer is crucial to achieve this goal. In recent years, the introduction of genome-wide profiling technologies including array-based comparative genomic hybridization, expression arrays, single-nucleotide polymorphism arrays, and more recently next generation sequencing has led to notable progress in our understanding of lung cancer biology. Some of these findings have had significant clinical implications such as the identification of the *EML4-ALK* fusion gene in patients with non-small cell lung cancer (NSCLC).[2] Treatment with crizotinib, a drug that targets this fusion gene results in striking responses in appropriately selected patients with NSCLC.[3] Nevertheless, this fusion gene is identified in less than 5% of all patients with NSCLC. Further studies are required to identify other such unique molecular changes that can be effectively targeted to treat patients with lung cancer. In the recently concluded 46th Annual Meeting of the American Society of Clinical Oncology, results from several studies related to lung cancer tumor biology or biomarkers were presented. We have identified some of the key presentations and summarized their findings in this brief review.

EPIDERMAL GROWTH FACTOR RECEPTOR

Somatic mutations in the kinase domain of epidermal growth factor receptor (*EGFR*) mutations, most commonly in exon 19 or 21, are the most reliable predictors for response to the *EGFR* tyrosine kinase inhibitors (TKIs), gefitinib and erlotinib.[4,5] K-*ras* is an important downstream mediator of *EGFR* signaling and is mutated in approximately 20% of patients with adenocarcinoma of the lung. As K-*ras* mutations are associated with decreased response rates and inferior outcomes in patients treated with *EGFR* TKIs, both *EGFR* and K-*ras* mutations are frequently evaluated as predictors for outcomes in patients with NSCLC.[6]

A retrospective study of 2080 patients with lung adenocarcinoma was conducted to evaluate the frequency of *EGFR* mutations and correlation with clinical variables.[7] *EGFR* mutations were found in 264 of 540 (49%) of never smokers, 149 of 1188 (13%) of former smokers, and 19 of 352 (5%) of current smokers. Mutations were also more common in women compared with men (23% versus 17%). The fact that *EGFR* mutations are present in men and in those with a history of smoking raises the question whether all patients with NSCLC should be tested for *EGFR* mutations.

Several polymerase chain reaction (PCR)/sequencing-based *EGFR* mutation detection assays are commercially available.[8] The turnaround time for many of these tests is several days, and the quality of the tumor samples may also limit their ability to detect the mutation. In a search for a

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rapid and sensitive assay for the detection of *EGFR* mutations using routine pathology specimens, 219 patients were tested for L858R mutation using real-time allele-specific PCR and for exon 19 deletions by length analysis of PCR products.[9] *EGFR* alterations were detected in 35 patients (16%), including 21 with exon 19 deletion (9.6%) and 14 with L858R mutation (6.4%). These procedures, performed in paraffin-embedded sections, had a rapid turnaround time of 24 hours.

In a retrospective study to evaluate the prognostic implication of *EGFR* and K-*ras* mutations in never smokers with lung adenocarcinoma, the clinical outcomes for 175 patients with early stage (stages I–IIIA) and 362 patients with advanced stage (IIIB or IV), there was a significant difference according to mutation status.[10] Among patients with early disease, 3-year survival was significantly better in those with *EGFR* mutation compared with wild type (86% versus 71%; $p = 0.02$) and in wild-type K-*ras* compared with mutant K-*ras* (81% versus 36%; $p = 0.001$). In advanced disease, although *EGFR* mutation was associated with improved survival (48% versus 29%; $p = 0.01$), the small survival improvement in wild-type K-*ras* was not statistically significant (40% versus 35%; $p = 0.3$).

Danenberg et al.[11] evaluated 838 specimens from patients with colorectal cancer and 1165 from patients with NSCLC for K-*ras* mutations and 649 specimens from patients with NSCLC for *EGFR* mutations. K-*ras* mutations were more common in patients with colorectal cancer than patients with NSCLC (39% versus 23%; $p < 0.001$). Previous studies have shown that exposure to tobacco smoke determines the type of Kras mutations identified in the tumor tissue.[12,13] K-*ras* mutations in tobacco smokers are more likely to be G→T transversions, whereas in never smokers G→A transition mutations are seen more frequently. The type of Kras mutation was also analyzed in this study by Danenberg and colleagues. As expected, K-*ras* mutations with tobacco smoking-related G→T transversions were more frequent in patients with NSCLC than patients with colorectal cancer (61% of all K-*ras* mutations versus 39%; $p < 0.001$). In the 447 tumor samples tested for both *EGFR* and K-*ras* mutations, the mutations were mutually exclusive in most, with only four specimens containing both mutations.

MET/VASCULAR ENDOTHELIAL GROWTH FACTOR/INSULIN-LIKE GROWTH FACTOR

Overexpression of *MET* (Mesenchymal Epithelial Transition Factor) has been reported in NSCLC, and the fact that it is phosphorylated in these tumors suggests that it is activated in NSCLC.[14,15] Resistance to *EGFR*-TKIs has also been associated with *MET* amplification.[16]

Cancer and Leukemia Group B conducted a study to correlate *MET* expression, phosphorylation, mutation, and amplification with survival in patients with resected adenocarcinoma. This project will also evaluate the correlation with other markers (*EGFR* and *P53* mutational status and level of expression, *KRAS* (Kristen Rat Sarcoma viral oncogene homolog) exon 2 mutational status, and epidermal-mesenchymal transition) and their impact on clinical outcomes. Interim results from 20 patients identified that the majority of them (95%) had high expression of *MET* by immunohistochemistry (IHC). Moreover, mutational analysis was performed in 40 patients, and previously unreported *MET* mutations were identified in three (7.5%) patients. Extended results and correlation with survival endpoints are awaited.[17]

Insulin-like growth factor receptor (IGF-1R) is associated with tumorigenesis, metastasis, and resistance to therapy in experimental models.[18] Nevertheless, a large phase III trial failed to demonstrate any benefit in unselected patients with NSCLC with the addition of an IGF-1R directed monoclonal antibody.[19]

Tissue microarrays of tumor tissue from patients with NSCLC were used to analyze protein expression patterns of *IGF* and *Src* genes.[20] The Src pathway has been shown to be a potential therapeutic target in NSCLC.[21] Tumor samples from two independent tissue banks ($n = 352$ and $n = 458$) were incorporated in the tissue microarrays. Expression levels of IGF-1R, IGF-1, IGF-2, phospho IGF-1R/IR, and phospho Src were measured by immunofluorescence ($p < 0.05$). The expression of these genes except for *IGF-1* was significantly higher in patients with squamous cell carcinoma than patients with adenocarcinoma ($p < 0.05$). Similarly, the expression of these genes was higher in tumor specimens from current smokers than from never smokers ($p < 0.05$). Results from this study also suggest that phospho Src expression may be an independent prognostic factor in patients with NSCLC, hazard ratio 1.02 (1.003–1.038) $p = 0.02$. Both IGF-1R and Src kinase pathways seem to be active in NSCLC particularly so in squamous cell carcinoma of the lung. Optimal patient selection and choosing appropriate agents that inhibit these promising pathways continue to be challenging.

EML4-ALK

EML4-ALK is the first fusion gene discovered in NSCLC.[2] The genes *EML4* and *ALK* are both located in chromosome 2 and the fusion results from an inversion within the chromosome. The *EML4-ALK* fusion gene is unique to NSCLC and has gain of function properties.[2,22,23] The *EML4-ALK* fusion gene is more frequently identified in younger patients with adenocarcinoma than older patients with other tumor histologies.[22,24–28] There is also a significant association with never smokers, and they seem to be mutually exclusive with *EGFR* and K-*ras* mutations. Crizotinib is a dual kinase inhibitor with activity against ALK kinase and C-met. In a recent phase I trial, patients with *EML4-ALK*-positive NSCLC treated with crizotinib had an overall response rate of 64% and disease control rate of 90%.[3] It is important to develop robust and easy to use diagnostic methods to detect *EML4-ALK* fusion gene when screening patients for treatment with crizotinib. Both fluorescent in situ hybridization (FISH) and PCR methods have been used to detect *EML4-ALK*, though FISH is being used in ongoing clinical trials with crizotinib.

Several groups have analyzed archived NSCLC tumor samples to describe the clinical characteristics and outcomes of patients with NSCLC harboring the *EML4-ALK* fusion gene.[29–33] The frequency of *EML4-ALK* fusion gene ranged

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TABLE 1. Clinical Characteristics of Patients with *EML4-ALK* Fusion Gene

	Kudo et al.[33]	Varella-Garcia et al.[32]	Soda et al.[31]	Danenberg et al.[29]	Rimkunas et al.[30]
N	492	447	384	130	656
Method	IHC	FISH	RT-PCR	RT-PCR	IHC/FISH
ALK positive	9 (1.8%)	12 (2.7%)	20 (5.2%)	6 (4.3%)	27 (4.1%)
Median age, yr (range)	53 (26–75)	66 (60–79)	50.9 (27–80)	—	—
Gender					
Male	3 (0.9%)	7 (1.6%)	5 (2%)	—	—
Female	6 (3.7%)	5 (1.1%)	15 (10.9%)	—	—
Histology					
Adeno	9 (3.5%)	12 (2.7%)	20 (7.9%)	—	—
Squamous	0	0	0	—	—
Smoking status					
Never smokers	6	4 (0.9%)	—	—	—
Smokers	3	8 (1.8%)	—	—	—

IHC, immunohistochemistry; FISH, fluorescent in situ hybridization; RT-PCR, reverse-transcriptase polymerase chain reaction.

TABLE 2. List of Mutated Genes in Pleural Mesothelioma

Genes	No. of Mutations (%)
BAP1	12 (22.6)
NF2	11 (19.6)
LATS2	4 (7.1)
RICTOR	4 (7.1)
TP53	4 (7.1)
CHEK2	2 (3.6)
LATS1	2 (3.6)
RB1	2 (3.6)
CDH5	1 (1.9)
CDKN3	1 (1.9)
ING1	1 (1.9)
PTPRD	1 (1.9)
RASSF1	1 (1.9)
SDHB	1 (1.9)
SMARCB1	1 (1.9)

BAP1, BRCA-associated protein 1; NF2, neurofibromatosis type 2.

between 2 and 5%, consistent with previous publications (Table 1). Furthermore, it was detected only in patients with adenocarcinoma histology.[31–33] In addition, efforts were made to develop newer diagnostic methods to detect *EML4-ALK* fusion gene.

An IHC-based assay using antibodies specific to the ALK kinase has been developed to detect *EML4-ALK* fusion gene.[30] To determine the accuracy of this method, FISH testing was done on a third of these tumor samples. There was complete correlation between IHC and FISH results. In another study, IHC was used to detect *EML4-ALK*, but the results were not compared with FISH or PCR.[33] Nevertheless, the results from this study on the prevalence and clinicopathologic characteristics of patients with *EML4-ALK* are consistent with previously reported studies. A multiplex reverse-transcriptase-PCR technique was reported to be effective in detecting *EML4-ALK* fusion gene in formalin-fixed paraffin-embedded (FFPE) samples using probes specifically designed to detect *EML4-ALK* fusion in FFPE samples.[29] Positive controls with cell lines that harbor *EML4-ALK* variants and negative control with A549 cell line that does not have the fusion gene were used to validate this PCR method. The authors report 100% specificity and sensitivity more than 99.9% in detecting the *EML4-ALK* fusion gene using this technique.

Even though current clinical trials are using FISH to detect *EML4-ALK* rearrangement, there are advantages to further developing and implementing the PCR and IHC assays. In addition, to identifying the fusion gene, PCR methods can quantify the fusion transcript and specify the type of *EML4-ALK* variant in a particular tumor sample. The IHC-based assay would be easy to use and can provide rapid diagnosis in relatively small tissue samples.

TUMOR GENOME PROFILING IN MESOTHELIOMA

Mesothelioma is a neoplasm arising in serosal cavities, and it is associated with asbestos exposure.[34,35] Mesothelioma is characterized by frequent deletion of *p16* (80%) gene and loss of heterozygosity in the neurofibromatosis type 2 gene (60%).[36,37] Patients with mesothelioma usually present with advanced stage disease, and the median survival ranges between 9 and 12 months.[38] Global genomic profiling was performed on 53 pleural mesothelioma tumors using expression and copy number arrays followed by targeted resequencing to identify new genetic changes.[39] Based on the global profiling, 25 genes were identified and were sequenced in the tumor samples. Of these 25 genes, mutations involving 15 genes were identified by sequencing in the tumor tissue and comparison with corresponding normal tissue was done for the majority of the samples (Table 2). Mutations involving the BRCA (breast cancer)-associated protein 1 (*BAP-1*) gene were identified in 12 (22.6%) tumor samples. It was confirmed by PCR in samples harboring the mutation. Validation was done in an additional 68 tumors samples, and *BAP-1* mutations were identified in 13 (19%) tumors. The exact role of *BAP-1* mutation is not known though it has been previ-

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ously identified in a small number of lung adenocarcinoma samples.[40] There was no correlation between *BAP-1* mutations status and survival, histology, or asbestos exposure. Further experiments are required to clarify the functional role of *BAP-1* mutation in pleural mesothelioma.

MOLECULAR CLASSIFICATION OF NSCLC

Histologic classification plays an important role in determining treatment choices for patients with NSCLC. Data from recent clinical trials have shown that only patients with nonsquamous histology are candidates for treatment with pemetrexed or bevacizumab.[41,42] Nevertheless, the medical oncologist is often faced with the dilemma of treating patients with tumors classified as NSCLC otherwise unspecified. In an effort to address this perennial problem, a protein-based assay was developed to differentiate between squamous and adenocarcinoma histologies in patients with NSCLC. In a training set of 343 NSCLC tumor samples, the expression of a panel of 24 proteins was compared between adenocarcinoma and squamous cell carcinoma using quantitative immunofluorescence.[43] A four-protein classifier was developed from this panel to differentiate between adenocarcinoma and squamous histologies. The pathologist's diagnosis was the gold standard against which the assay was compared. The assay had a sensitivity of 96% and specificity of 93% in the training set. The assay was then validated by blinded analysis in two independent cohorts: a retrospectively collected cohort (n = 197) and a prospectively collected cohort (n = 235). The assay had a sensitivity of 92% and specificity of 97% to differentiate between squamous versus adenocarcinoma histology in the retrospective cohort. In the prospective cohort, the assay yielded a sensitivity and specificity of 96% and 97%, respectively. These results show the feasibility of developing molecular tests that can aid in histologic classification of NSCLC. As histology guides treatment decision in patients with NSCLC, such a test can be a valuable addition to the clinician.

SUMMARY

The identification of *BAP-1* mutation in pleural mesothelioma is a novel discovery, and further studies are required to clarify the functional role of this mutation. The fact that *EML4-ALK* is found exclusively in patients with adenocarcinoma is an important finding that would help the clinician screening patients for ongoing clinical trials on crizotinib and identify patients who are likely to harbor the fusion gene. Using IHC to detect the *EML4-ALK* fusion gene (if validated in further studies) could be useful in cases where sufficient tissue is not available for FISH or PCR. The development of a robust assay using PCR for detection of the *EGFR*-tyrosine kinase mutation from FFPE samples would be useful in the clinic to rapidly and accurately identify the presence of the mutation. The role of IGF, Src, vascular endothelial growth factor, and *MET* as therapeutic targets or as biomarkers requires further investigation.

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