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ORIGINAL REPORT

Clinical Features and Outcome of Patients With Non–Small-Cell Lung Cancer Who Harbor *EML4-ALK*

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The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

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ABSTRACT

Purpose
The *EML4-ALK* fusion oncogene represents a novel molecular target in a small subset of non–small-cell lung cancers (NSCLC). To aid in identification and treatment of these patients, we examined the clinical characteristics and treatment outcomes of patients who had NSCLC with and without *EML4-ALK*.

Patients and Methods
Patients with NSCLC were selected for genetic screening on the basis of two or more of the following characteristics: female sex, Asian ethnicity, never/light smoking history, and adenocarcinoma histology. *EML4-ALK* was identified by using fluorescent in situ hybridization for *ALK* rearrangements and was confirmed by immunohistochemistry for ALK expression. *EGFR* and *KRAS* mutations were determined by DNA sequencing.

Results
Of 141 tumors screened, 19 (13%) were *EML4-ALK* mutant, 31 (22%) were *EGFR* mutant, and 91 (65%) were wild type (WT/WT) for both *ALK* and *EGFR*. Compared with the *EGFR* mutant and WT/WT cohorts, patients with *EML4-ALK* mutant tumors were significantly younger ($P < .001$ and $P = .005$) and were more likely to be men ($P = .036$ and $P = .039$). Patients with *EML4-ALK*–positive tumors, like patients who harbored *EGFR* mutations, also were more likely to be never/light smokers compared with patients in the WT/WT cohort ($P < .001$). Eighteen of the 19 *EML4-ALK* tumors were adenocarcinomas, predominantly the signet ring cell subtype. Among patients with metastatic disease, *EML4-ALK* positivity was associated with resistance to EGFR tyrosine kinase inhibitors (TKIs). Patients in the *EML4-ALK* cohort and the WT/WT cohort showed similar response rates to platinum-based combination chemotherapy and no difference in overall survival.

Conclusion
EML4-ALK defines a molecular subset of NSCLC with distinct clinical characteristics. Patients who harbor this mutation do not benefit from EGFR TKIs and should be directed to trials of ALK-targeted agents.

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INTRODUCTION

Lung cancer is the leading cause of cancer deaths in the world, as greater than 1 million deaths from lung cancer occur each year.[1] Although cytotoxic chemotherapy remains the mainstay of treatment for the majority of patients with advanced non–small-cell lung cancer (NSCLC),[2,3] tyrosine kinase–based therapeutics have assumed an increasingly important role, particularly in genetically defined subsets of patients. For example, activating mutations in the receptor tyrosine kinase epidermal growth factor receptor (*EGFR*) define a small subset of patients with NSCLC who have sensitivity to EGFR tyrosine kinase inhibitors (TKIs), such as gefitinib or erlotinib.[4,5] In mutation-positive patients with previously untreated, advanced disease, gefitinib recently has been shown to be superior to cytotoxic chemotherapy.[6] The remarkable success of EGFR TKIs highlights the importance of identifying genotype-specific subsets of patients to guide the appropriate selection of targeted therapies.

The *EML4-ALK* fusion oncogene represents one of the newest molecular targets in NSCLC. First described in 2007,[7,8] the fusion results from a small inversion within chromosome 2p, which leads to expression of a chimeric tyrosine kinase, in which the N-terminal half of echinoderm

microtubule-associated protein-like 4 (EML4) is fused to the intracellular kinase domain of anaplastic lymphoma kinase (ALK).[9] EML4-ALK possesses potent oncogenic activity both in vitro and in vivo.[7,10] This activity can be effectively blocked by small-molecule inhibitors that target ALK,[10,11] which supports a role for EML4-ALK as a key driver of lung tumorigenesis.

Several studies have examined the frequency of *EML4-ALK* in patients with NSCLC. In the original report of *EML4-ALK*, five of 75 lung tumors demonstrated expression of the fusion transcript, which corresponded to a frequency of 6.7%.[7] In subsequent studies that primarily involved Asian patients with early-stage, resectable disease, *EML4-ALK* has been detected in a lower percentage of patients, which ranged from 1% to 4.9%.[8,11-17] These findings suggest that, in unselected NSCLC populations, the *EML4-ALK* rearrangement is a relatively rare event. In part because of the small number of positive instances identified per study, the key pathologic, epidemiologic, and demographic features associated with *EML4-ALK* have not been definitively established. Furthermore, whether patients with this chromosomal rearrangement share similar outcomes to other genetically defined subsets of NSCLC, particularly in the metastatic setting, also is unknown.

Here, we present the largest series to date of *EML4-ALK*–positive patients with NSCLC. We describe the clinical and pathologic characteristics of patients with *EML4-ALK*, and we also examine treatment response and survival in patients who have metastatic disease with and without *EML4-ALK*.

PATIENTS AND METHODS

Study Population

The majority of patients were seen at the Massachusetts General Hospital Cancer Center. Three patients were observed at the Beth Israel Deaconess Medical Center, and one patient was observed at the Peter MacCallum Cancer Centre. Patients were selected for genetic screening on the basis of two or more of the following clinical characteristics: female sex, Asian ethnicity, never/light smoking history (defined in Table 1), and adenocarcinoma histology. All study patients had biopsy-proven NSCLC, and the majority of patients had metastatic disease. Patients with insufficient tissue for genetic testing, or for whom *EML4-ALK* fluorescent in situ hybridization (FISH) was inconclusive, were excluded. This study was approved by the institutional review boards at each of the participating centers.

Data Collection

For all patients, medical records were reviewed to extract data on clinicopathologic characteristics. For patients with stage IV disease at the time of genetic screening, we examined treatment regimens, response rates, and outcomes. Patients with multifocal bronchioloalveolar carcinoma (BAC) were excluded from this analysis. In the majority of patients, interval computed tomography scans were available for review by one thoracic radiologist. Responses were classified by using standard RECIST (Response Evaluation Criteria in Solid Tumors).[18] Time to progression (TTP) was measured from the first day of treatment until radiologic or clinical progression. Overall survival (OS) was measured from the date of diagnosis of metastatic NSCLC until the date of death. Patients without a known date of death were censored at the time of last follow-up.

Tumor Pathology and Mutation Analysis

Tumor histology was classified by using WHO criteria.[19] To identify *ALK* rearrangements, FISH was performed on formalin-fixed, paraffin-embedded tumors by using a break-apart probe to *ALK* (Vysis LSI ALK Dual Color, Break Apart Rearrangement Probe; Abbott Molecular, Abbott Park, IL; Fig 1A). All FISH-positive occurrences (defined as > 15% of tumor cells with split signals) were confirmed by immunohistochemistry (IHC) by using a mouse monoclonal antibody against *ALK* (clone ALK1; DAKO USA, Carpinteria, CA; Fig 1B). A subset of FISH-positive occurrences also was confirmed by reverse transcriptase polymerase chain reaction (Fig A1). *EGFR* and *KRAS* mutations were determined by direct DNA sequencing.

Table 1. Clinical Characteristics of Genetically Screened Patients With Non–Small-Cell Lung Cancer

Characteristic	Patients (N = 141) No.	%
Age, years		
Median	63	
Range	29-90	
Sex		
Male	48	34
Female	93	66
Smoking history†		
Never smoker	59	42
Light smoker	26	18
Smoker	56	40
Ethnicity		
Asian	9	6
Non-Asian	132	94
Pathology		
Adeno	89	63
BAC*	41	29
Adenosquamous	4	3
Squamous	2	1
Large cell/NOS	5	4
Stage‡		
IA	14	10
IB	11	8
IIA	1	1
IIB	0	0
IIIA	5	4
IIIB	4	3
IV	96	68
Multifocal BAC	10	7

Abbreviations: adeno, adenocarcinoma; BAC, bronchioloalveolar carcinoma; NOS, not otherwise specified.
*Adenocarcinoma with any element of BAC was listed as BAC.
†Never smokers have smoked < 100 cigarettes in their lifetime; light smokers have smoked ≤ 10 pack years; and smokers have smoked > 10 pack years.
‡Clinical stage represents stage at time of mutation testing. Stage was determined according to current American Joint Commission on Cancer guidelines; however, patients with malignant pleural effusions were classified as stage IV.

Statistical Analysis

For clinical characteristics, treatment types, and response rates, Fisher's exact test was used to assess the association of genotype with dichotomous factors, whereas the Wilcoxon rank sum test was applied to continuous data. The Kaplan-Meier method was used to estimate TTP and OS, and the difference between genotypes was compared by using the log-rank test. General data analysis was conducted with SAS 9.1 (SAS Institute, Cary, NC), whereas StatXact 6.1 (Cytel Software, Cambridge, MA) was used to compute exact *P* values. All *P* values were based on a two-sided hypothesis.

RESULTS

Between November 2007 and October 2008, we screened 141 patients with NSCLC for *ALK* rearrangements, hereafter referred to as *EML4-ALK*. The criteria used to select patients for genetic screening were

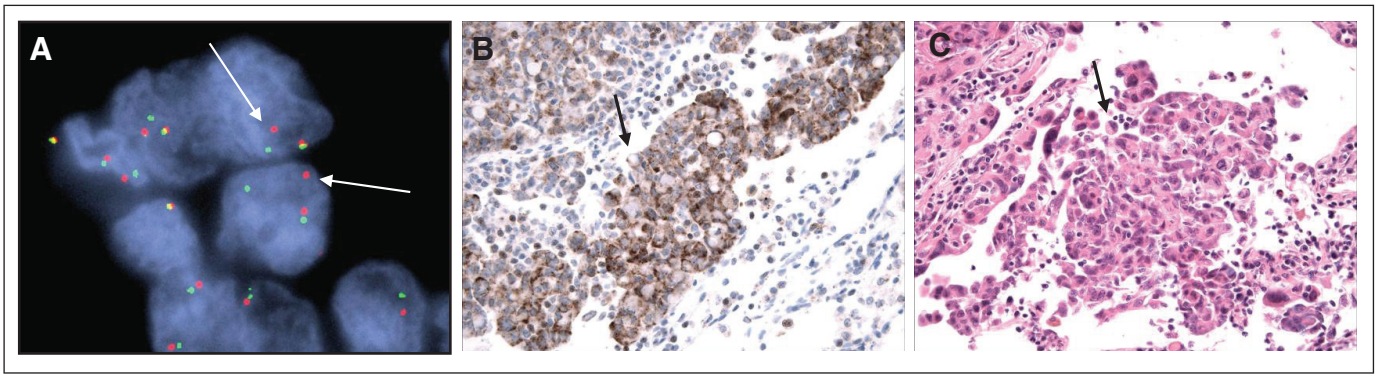

Fig 1. Diagnostic features of *EML4-ALK*–positive non–small-cell lung cancer (NSCLC). (A) Fuorescent in situ hybridization (FISH) reveals a split of red and green probes that flank the *ALK* translocation site in an *EML4-ALK*–positive tumor (arrows). (B) *ALK* immunohistochemistry reveals cytoplasmic *ALK* staining. (C) Hematoxylin and eosin staining of the same tumor. Arrows in (B) and (C) indicate signet ring cells, which are commonly found in *EML4-ALK*–positive tumors.

based on clinical features commonly associated with *EGFR* mutation.[20,21] As a result, the cohort of screened patients was enriched for women, for never/light smokers, and for patients with adenocarcinomas or adenocarcinomas with bronchioloalveolar features (ie, BAC; Table 1). This enrichment strategy was chosen to target the population of never/light smokers and to enable identification of patients who harbored either *EML4-ALK* or *EGFR* mutation within the same study group.

Table 2. Clinical Characteristics of Genotype-Specific Subsets of Patients With Non–Small-Cell Lung Cancer

	Genotype						*P*	
	ALK (n = 19)		*EGFR* (n = 31)		WT/WT (n = 91)			
Characteristic	No.	%	No.	%	No.	%	*ALK v EGFR*	*ALK v* WT/WT
Age, years								
Median	52		66		64		< .001	.005
Range	29-76		36-90		29-87			
Sex								
Male	11	58	8	26	29	32	.036	.039
Female	8	42	23	74	62	68		
Smoking history								
Never smoker	14	74	21	68	24	26	.366	< .001
Light smoker	5	26	6	19	15	16		
Smoker	0	0	4	13	52	57		
Ethnicity								
Asian	0	0	2	6	7	8	.519	.602
Non-Asian	19	100	29	94	84	92		
Pathology								
Adeno	16	84	24	77	49	54	.380*	.686*
BAC†	2	11	7	23	32	35		
Adenosquamous	1	5	0	0	3	3		
Squamous	0	0	0	0	2	2		
Large cell/NOS	0	0	0	0	5	6		
Stage								
IA	2	11	2	6	10	11		
IB	0	0	1	3	10	11		
IIA	0	0	0	0	1	1		
IIB	0	0	0	0	0	0		
IIIA	0	0	2	6	3	3		
IIIB	0	0	0	0	4	4		
IV	17	89	26	84	53	58	.695‡	.051‡
Multifocal BAC	0	0	0	0	10	11		

Abbreviations: WT, wild type; adeno, adenocarcinoma; BAC, bronchioloalveolar carcinoma; NOS, not otherwise specified.
*Adeno and BAC *v* all others.
†Adeno with any element of BAC is listed as BAC.
‡Stages I to III *v* IV.

Table 3. Mutation Analysis of Screened Patients With Non–Small-Cell Lung Cancer

Analysis	Genotype		
	ALK	*EGFR*	WT/WT
ALK rearrangement			
Positive	19	0	0
Total	19	31	91
EGFR mutation			
Positive	0	31	0
Total	19	31	74
KRAS mutation*			
Positive	0	0	6
Total	11	10	23

Abbreviation: WT, wild type.
**KRAS* mutation testing was not performed on all patients because of limited amounts of tissue.

Clinicopathologic Characteristics of EML4-ALK*–Positive Patients*

Of the 141 tumors screened, 19 (13%) harbored the *EML4-ALK* rearrangement, 31 (22%) harbored an activating *EGFR* mutation, and 91 (65%) were wild type for both *ALK* and *EGFR* (designated WT/WT). Of note, this WT/WT cohort included at least six patients with activating *KRAS* mutations (Table A1). Compared with patients who had *EGFR* mutant and WT/WT, *EML4-ALK*–positive patients were significantly younger; the median age was 52 years in *EML4-ALK*–positive patients compared with 66 years in patients with *EGFR* mutation and 64 years in patients with WT/WT status (Table 2; $P < .001$ and $P = .005$, respectively). *EML4-ALK*–positive patients also were more likely than either *EGFR* or WT/WT patients to be men (Table 2; $P = .036$ and $P = .039$, respectively). Although the *EML4-ALK* fusion oncogene was first discovered in a patient with a history of smoking,[7] the *EML4-ALK*–positive patients in this series, like the *EGFR* patients, were significantly more likely to be never/light smokers compared with the WT/WT patients ($P < .001$).

Because requests for genetic screening originated primarily from medical oncology clinics, the majority of patients had metastatic disease at the time of screening (Table 1). Within the *EML4-ALK* cohort, 17 (89%) of 19 had stage IV disease. Similarly, 26 (84%) of 31 patients with *EGFR* mutations had stage IV disease (Table 2; $P = .695$). Only 53 (58%) of 91 WT/WT patients had metastatic disease, which suggests a trend toward higher clinical stage among *EML4-ALK*–positive patients compared with WT/WT patients ($P = .051$). The majority of screened patients also had adenocarcinoma, including adenocarcinoma with BAC features (Table 1). Of the 19 *EML4-ALK*–positive

Table 4. Summary of Treatments and Responses by Genotype in Metastatic Non–Small-Cell Lung Cancer

Variable	Genotype						*P*	
	ALK (n = 15)		*EGFR* (n = 25)		WT/WT (n = 49)			
	No.	%	No.	%	No.	%	*ALK v EGFR*	*ALK v* WT/WT
No. of treatment regimens								
Median	3		1		2		.083	.178
Range	1-4		1-6		0-9			
Type of treatment								
Chemotherapy*	12	80	9	36	37	76	.010	1.000
EGFR TKI	10	67	24	96	23	47	.021	.254
Best response to chemotherapy*								
No. of patients evaluated	12		8†		34‡			
CR	0	0	0	0	0	0		
PR	3	25	4	50	12	35		
SD	7	58	3	38	19	56		
PD	2	17	0	0	2	6		
Unevaluable§	0	0	1	13	1	3		
Best response to TKI								
No. of patients evaluated	10		23†		23			
CR	0	0	1	4	0	0		
PR	0	0	15	65	3	13		
SD	4	40	6	26	7	30		
PD	6	60	0	0	11	48		
Unassessable§	0	0	1	4	2	9		
Response rate, %								
Chemotherapy*	25		50		35		.356	.723
TKI	0		70		13		< .001	.536

NOTE. Patients with no documentation of treatment history were excluded from this analysis.
Abbreviations: WT, wild type; EGFR TKI, epidermal growth factor receptor tyrosine kinase inhibitor; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.
*Chemotherapy refers specifically to a platinum-based combination chemotherapy regimen.
†Excludes chemotherapy plus TKI (n = 1).
‡Excludes chemotherapy plus radiation therapy (n = 3).
§No assessment because of early death, short follow-up, or lack of documentation.

tumors, 18 were adenocarcinomas, and one was a mixed adenosquamous carcinoma. Interestingly, compared with either *EGFR* mutant or WT/WT tumors, *EML4-ALK*–positive tumors were significantly more likely to have abundant signet ring cells (defined as ≥ 10% of tumor cells; Fig 1C). In addition, among the evaluable adenocarcinomas that harbored *EML4-ALK*, 61% showed solid growth as the predominant pattern, whereas acinar growth and BAC patterns were seen in only 31% and 8%, respectively.

Molecular Genotyping of Patients

Consistent with previous studies, which showed that *EML4-ALK* and *EGFR* mutation are mutually exclusive,[7,15,17] we identified no *EGFR* mutations in the *EML4-ALK* cohort and no instances of *ALK* rearrangement in the *EGFR* cohort (Table 3). Similarly, among the patients screened for *KRAS* mutation, we found six positive patients in the WT/WT cohort, but none in either the *EML4-ALK* or *EGFR* mutant cohorts (Table 3; $P = .022$). These findings demonstrate that the molecular subsets of NSCLC defined by *EML4-ALK*, *EGFR*, or *KRAS* mutations are distinct and nonoverlapping.

Treatment Response and Clinical Outcome of Patients With and Without EML-ALK

We determined best clinical response after treatment with an EGFR TKI or a platinum-based chemotherapy regimen in patients with metastatic disease. Among 10 patients with *EML4-ALK* and with evaluable disease, none had a documented clinical response to erlotinib (Table 4). Four patients (40%) had stable disease (SD), and six patients (60%) had progressive disease (PD) on erlotinib. In the WT/WT cohort, three (13%) of 23 treated patients had a partial response (PR), seven (30%) had SD, and 11 (48%) had PD on gefitinib or erlotinib. The small difference in response rates between *EML4-ALK* and WT/WT patients treated with an EGFR TKI was not statistically significant ($P = .536$). By contrast, 16 (70%) of 23 patients with *EGFR* mutations had a documented clinical response to an EGFR TKI. The higher response rate of *EGFR* mutation–positive patients compared with *EML4-ALK*–positive or WT/WT patients was highly statistically significant ($P < .001$).

To evaluate response to platinum-based chemotherapy, we examined all metastatic patients who had received carboplatin or cisplatin in combination with one or more therapeutic agents. These agents included standard chemotherapies, such as taxanes, as well as targeted agents, such as bevacizumab. Patients who had previously received a platinum combination as adjuvant therapy were excluded from this analysis. Within the *EML4-ALK* cohort, three (25%) of 12 evaluable patients had a PR, seven (58%) had SD, and two (17%) had PD on platinum-based chemotherapy (Table 4). A similar response was seen among 34 treated, WT/WT patients: 12 (35%) had PRs, 19 (56%) had SD, and two (6%) had PD ($P = .723$). Compared with patients who harbored *EGFR* mutations, *EML4-ALK*–positive patients showed a lower response rate to platinum-based chemotherapy, but this difference was not statistically significant ($P = .356$).

At the time of review, median follow-up of patients with metastatic NSCLC was 13 months among the 55 patients (57%) still alive; at that time, 39 patients (41%) had died, and two patients (2%) had been lost to follow-up. We analyzed both TTP and OS of patients according to genotype. For *EML4-ALK*–positive patients treated with an EGFR TKI, the median TTP was only 5 months, compared with 6 months for WT/WT patients ($P = .337$) and 16 months for patients with *EGFR* mutation ($P = .004$; Fig 2A). The median TTP for patients who received platinum-based chemotherapy was in the same range of 8 to 10 months across all three genotypes (Fig 2B). The median OS of *EML4-ALK* patients was 20 months, compared with 32 months for patients with *EGFR* mutation and 16 months for WT/WT patients, although these differences were not statistically significant ($P = .468$ and $P = .152$; Fig 2C).

DISCUSSION

The *EML4-ALK* translocation defines a new molecular subset of NSCLC with distinct clinical and pathologic features. Previous studies have reported a low frequency of *EML4-ALK* that has ranged from

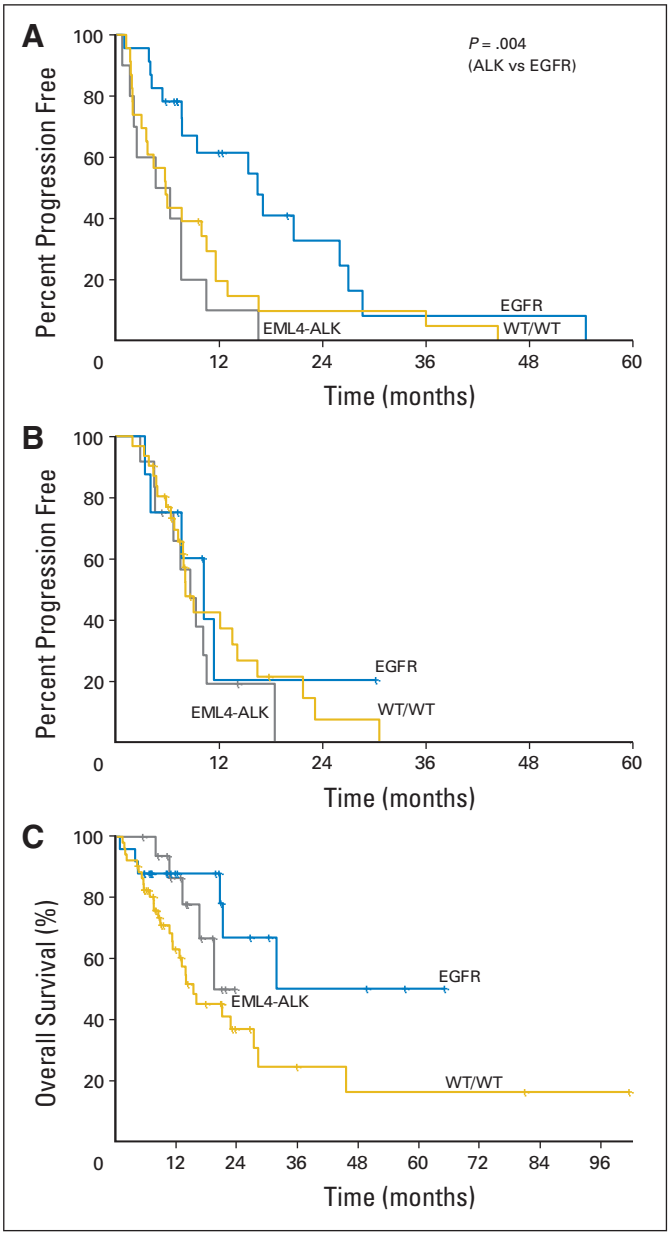

Fig 2. Time to progression (TTP) and overall survival (OS) of *EML4-ALK*–positive patients compared with patients who have *EGFR* mutant and wild-type (WT)/WT tumors. (A) TTP on epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor monotherapy. (B) TTP on any first-line, platinum-based, combination regimen. (C) Kaplan-Meier survival plots of OS.

1.5% to 6.7% in unselected populations.[7,11,13-17] These studies have involved predominantly Asian patients with surgically resected disease. In this study, we show that, in a select subpopulation of predominantly white patients, the majority of whom had metastatic NSCLC, the frequency of *EML4-ALK* is significantly higher than that reported for unselected patients. Among the 141 patients screened, we identified 19 with *EML4-ALK* and 31 with *EGFR* mutation, which corresponded to frequencies of 13% and 22%, respectively. Within the group of never/light smokers in this study, the frequencies of *EML4-ALK* and *EGFR* were 22% and 32%, respectively; among never/light smokers without *EGFR* mutation, the frequency of *EML4-ALK* was 33%. These findings suggest that, in patients with NSCLC who have clinical characteristics associated with *EGFR* mutation but who have negative *EGFR* testing, as many as one in three patients may harbor *EML4-ALK*.

Previous reports that describe the frequency of *EML4-ALK* in NSCLC have been inconsistent in terms of clinical features that define this molecular subset. For example, in the first report of *EML4-ALK* in NSCLC, *ALK* rearrangement was detected in five patients, two of whom were noted to have a smoking history.[7] In subsequent studies, *EML4-ALK* has been variably detected in both smokers and nonsmokers,[8,11,15,16] which suggests a lack of association between smoking history and presence of *EML4-ALK*. Here, 19 of 85 patients classified as never/light cigarette smokers were positive for *EML4-ALK*, whereas all 56 patients with a smoking history (> 10 pack years) were negative. This result suggests that *EML4-ALK* is, in fact, strongly associated with never/light smoking history. This association was likely obscured in other studies because of small sample sizes and, possibly, differences in ethnic background.

Although *EML4-ALK* patients share several clinical features with patients who have *EGFR* mutant, including never/light smoking history and adenocarcinoma histology, this study demonstrates that *EML4-ALK* is associated with at least three distinct features. First, compared with *EGFR* or WT/WT patients, *EML4-ALK* patients are more likely to be men. As female sex was used as one of the clinical selection criteria for genetic screening, our study tested almost twice as many women as men. However, we found that a significantly greater percentage of men than women were positive for *EML4-ALK* (23% *v* 9%). The sex difference observed in this study cannot be explained by differences in smoking history, as 60% of men and 60% of women were never/light smokers. Second, compared with *EGFR* or WT/WT patients, *EML4-ALK* patients are significantly younger. The difference in median age between *EML4-ALK* patients and either *EGFR* or WT/WT patients exceeded 10 years. Of note, the median age of our *EGFR* cohort was similar to that reported in other studies.[22-24] Among the 19 patients with *EML4-ALK*, four were younger than 40 years old. One recent study of *EML4-ALK* in Asian patients with NSCLC noted a nonstatistically significant trend toward younger median age.[17] Interestingly, several other cancers known to harbor *ALK* rearrangements, such as anaplastic large cell lymphomas, neuroblastomas, and inflammatory myofibroblastic tumors, are also associated with younger age and are, in fact, most common in children and young adults. Third, *EML4-ALK*–positive tumors appear histologically distinct from *EGFR* mutant and WT/WT tumors. The diagnostic and clinical implications of this finding will be discussed in a separate report (Rodig et al, manuscript submitted for publication), but this observation suggests that *EML4-ALK* may represent a unique pathologic subtype of nonsmoking-related NSCLC.

In the clinic, the distinction between *EML4-ALK* and *EGFR* mutant tumors has important therapeutic implications. Whereas *EGFR* mutation confers sensitivity to EGFR TKIs, *EML4-ALK* is strongly associated with resistance. Among the 19 patients in this study with any response to erlotinib or gefitinib, 16 (84%) harbored an activating *EGFR* mutation, whereas none harbored *EML4-ALK*. Conversely, among the 34 patients refractory to EGFR TKIs, 10 (29%) were positive for *EML4-ALK*. These findings are consistent with preclinical studies, which showed that the *EML4-ALK*–containing NSCLC cell line H3122 is resistant to erlotinib.[11] These findings are also reminiscent of the resistance to EGFR TKIs conferred by activating mutations in *KRAS*.[25] However, whereas *KRAS* mutations are more commonly found in smokers,[26] both *EML4-ALK* and *EGFR* mutations are found in a similar population of never/light smokers. As a result, in the absence of genetic testing, *EML4-ALK* patients are likely to be treated like patients with *EGFR* mutation. Indeed, in this study, five of 15 *EML4-ALK* patients with metastatic NSCLC received erlotinib in the first-line setting. These results illustrate the importance of pretreatment genetic testing to guide clinical treatment recommendations, especially with regard to EGFR TKIs.

Overall, the clinical response of *EML4-ALK* patients more closely resembles that of WT/WT patients rather than patients with *EGFR* mutation. Both *EML4-ALK* and WT/WT patients are unlikely to respond to EGFR TKIs and have lower rates of response to platinum-based chemotherapy than patients with *EGFR* mutation. This difference does not appear to be related to imbalances among the cohorts in terms of type of platinum or inclusion of bevacizumab. The higher response rate associated with *EGFR* mutation is consistent with previous studies, including the recently presented IPASS study (IRESSA Pan Asia Study), in which clinically selected patients with metastatic NSCLC were randomly assigned in the first-line setting to either carboplatin/paclitaxel or gefitinib. Among patients treated with chemotherapy, the objective response rates were 47.3% in *EGFR* mutation–positive patients and 23.5% in *EGFR* mutation–negative patients.[6] This study suggests that *EML4-ALK*, in contrast to *EGFR* mutation, is not associated with enhanced chemosensitivity.

Previous studies have not examined the outcome of patients with NSCLC who harbor *EML4-ALK*. Here, we evaluated outcome by determining TTP and OS among patients with metastatic disease. This analysis was limited by the retrospective design of the study, by the relatively short duration of follow-up, and by the small number of events in the mutant cohorts. Nevertheless, *EML4-ALK* patients had a longer median survival compared with WT/WT patients, though the power was too low to detect a significant difference. Patients who harbored *EGFR* mutations showed a statistically significant improvement in survival compared with WT/WT patients ($P = .018$), which is consistent with previous reports that demonstrated a more favorable outcome among patients with *EGFR* mutation.[27] This survival analysis is additionally complicated by baseline differences in demographic features, particularly age and smoking history, between *EML4-ALK*–positive and –negative patients, as well as by differences in the number and types of therapies received. In addition, to date, seven of 17 *EML4-ALK* patients with metastatic disease have participated in a phase 1 study of PF-02341066, a dual *MET/ALK* TKI.[28] The clinical activity of this novel agent has not yet been reported, but its use in a significant proportion of *EML4-ALK* patients may have influenced the outcome of this cohort.

In conclusion, *EML4-ALK* defines a new molecular subset of NSCLC with distinct clinical and pathologic features. The patients most likely to harbor *EML4-ALK* are young, never/light smokers with adenocarcinoma. As some of these features are also associated with *EGFR* mutation, it is essential to screen such patients by mutation testing and not to rely solely on the presence of clinical predictors. We recommend screening first for *EGFR* mutation, because *EGFR* mutations are more common

than *EML4-ALK* rearrangements and because, importantly, EGFR TKIs are now used as first-line agents in advanced, mutation-positive disease. In the absence of an *EGFR* mutation, patients then should be screened for *EML4-ALK*. Preclinical studies have shown that *EML4-ALK* confers sensitivity to *ALK* inhibitors,[10,11,29] and studies suggest that patients with this chromosomal translocation may derive clinical benefit from specific *ALK* inhibition. This hypothesis currently is being tested in the clinic and if confirmed will validate *ALK* as a therapeutic target in NSCLC.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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