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Clinical outcomes of patients with resected, early-stage ALK-positive lung cancer

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Abstract

Objectives—Reports of the prognostic significance of *ALK*-rearrangement in resected non-small cell lung cancer (NSCLC) have been contradictory. We aimed to determine the prognosis of early-stage *ALK*-positive lung cancers relative to *KRAS*- and *EGFR*-mutant lung cancers.

Material and Methods—We reviewed medical records of patients with resected NSCLC harboring an *ALK* rearrangement (n=29) or a driver mutation in *EGFR* (n=255) or *KRAS* (n=480). Recurrence-free survival (RFS) was estimated for each genotype with the differences reported as a hazard ratio (HR).

Results—Among the 764 patients, 555 (73%), 101 (13%), and 108 (14%) had stage I, II, and III NSCLC, respectively. *ALK*-positive patients were distributed across all stages: 10 (34%) stage I, 6 (21%) stage II, and 13 (45%) stage III. Median RFS was not reached for *EGFR*-mutant patients, 24.3 months (95%CI 11.4 to 65.3) for *ALK*-positive patients, and 72.9 months (95%CI 59.7 to undefined) for *KRAS*-mutant patients. When adjusted for stage, *ALK*-positive NSCLC remained

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Conflicts of Interest

JEC has served as a compensated consultant or received honoraria from Bristol Myers Squibb, AstraZeneca, Genentech, and Merck. IDJ has served as a compensated consultant or received honoraria from Boehringer-Ingelheim and Foundation Medicine. ATS has served as a compensated consultant or received honoraria from Pfizer, Novartis, Genentech/Roche, Ariad/Takeda, Loxo, Blueprint, Foundation Medicine, Ignyta, and KSQ Therapeutics. JFG has served as a compensated consultant or received honoraria from Pfizer, Genentech/Roche, Novartis, Bristol-Myers Squibb, Merck, Incyte, Ariad, Loxo, and Clovis Oncology. The remaining authors have nothing to disclose.

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associated with worse RFS compared to *EGFR*-mutant (HR 1.8, 95%CI: 1.1–3.1), but not when compared to *KRAS*-mutant (HR 1.3, 95%CI: 0.8–2.1) NSCLC.

Conclusions—In this large series of resected NSCLC, *ALK* rearrangements were associated with a trend toward inferior disease outcomes compared to other clinically relevant genomic subsets. These data support the need for clinical trials evaluating use of ALK inhibitors among *ALK*-positive patients with localized or locally-advanced disease.

Keywords

ALK-rearrangement; early-stage non-small cell lung cancer

INTRODUCTION

Lung cancers driven by oncogenic rearrangements involving the anaplastic lymphoma kinase (*ALK*) gene represent a rare but clinically relevant subset of non-small cell lung cancer (NSCLC).[1] Sequential use of an ever-expanding repertoire of highly effective ALK inhibitors has significantly improved outcomes for patients with metastatic *ALK*-positive NSCLC.[2] However, the widespread use of ALK inhibitors has also affected our ability to study the prognostic relevance of this predictive biomarker. Despite being an established therapeutic target in the metastatic setting, the rarity of *ALK* rearrangements in non-metastatic disease poses a challenge to clinical studies of ALK inhibitors in the resectable or locally advanced setting. Theoretically, determining the prognostic impact of *ALK* status should be more straightforward in the early-stage setting given the absence of approved targeted therapies. Yet, the few published studies of resectable *ALK*-positive NSCLC have had conflicting results, likely due to inclusion of molecularly heterogeneous comparator groups.[3–6]

Given the limitations of the current literature, we undertook this pooled retrospective analysis to better understand the prognostic implications of *ALK* rearrangement. Outcomes of patients with resected *ALK*-positive tumors were compared to two other clinically relevant cohorts: patients with resected tumors harboring activating mutations in the epidermal growth factor receptor gene (*EGFR*) and Kirsten rat sarcoma virus gene (*KRAS*).

MATERIALS AND METHODS

Study Population

Patients (n=764) with surgically resected Stage I–III (American Joint Committee on Cancer 7th edition) NSCLC harboring an *EGFR* or *KRAS* mutation or an *ALK* rearrangement were identified from the charts of consecutive patients that underwent resection at Massachusetts General Hospital or Memorial Sloan Kettering Cancer Center between January 2009 and December 2012. This study was approved by the Institutional Review Board at both institutions.

Data Collection

Data were extracted from medical records, updated as of December 2016. Recurrence-free survival (RFS) was measured from the date of surgery to the date of death or development of

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relapse. Overall survival (OS) was measured from the date of surgical resection. For cases without events, RFS and/or OS were censored at the time of last follow-up.

Tumor Pathology and Genetic Analysis

Tumor histology was defined using World Health Organization criteria. *ALK* rearrangements were identified using a dual-color break-apart fluorescence *in situ* hybridization assay. Mutations in *EGFR* and *KRAS* were detected by one of two next-generation sequencing platforms: MSK-IMPACT, a hybridization capture-based assay,[7] and SNaPshot, an anchored multiplex polymerase chain reaction-based assay.[8]

Statistical Analysis

Fisher's exact test was used to compare categorical characteristics between genotypes, while age was analyzed by Wilcoxon rank-sum test. The Kaplan-Meier method was used to estimate the distributions of RFS and OS. The proportional hazards model was used to estimate the hazard ratio (HR) for assessing RFS and OS differences between genotypes adjusting for stage at diagnosis, with the 95% confidence interval constructed by the Wald method. Data analysis was performed using SAS 9.4 (SAS Inst Inc, Cary, NC), with all p-values based on a two-sided hypothesis.

RESULTS

Patient Characteristics

We identified 764 patients, the baseline characteristics of which are summarized in Table 1. Of the 764 patients, 29 (4%) were *ALK*-positive, whereas 480 (63%) and 255 (33%) were *KRAS*- and *EGFR*-mutant, respectively. Patients with *ALK*-positive tumors were distributed across all stages: 10 (34%) stage I, 6 (21%) stage II, and 13 (45%) stage III. Patients with *ALK*-positive NSCLC were younger with a lesser smoking history compared to those with *KRAS*-mutant NSCLC (p= < 0.001), and had a more even gender distribution compared to patients with *EGFR*-mutant NSCLC (p= 0.013).

Recurrence-Free Survival

With median follow-up of 60.5 months (range: 0.1 to 89.7), 235 (31%) patients relapsed. Eighteen (8%) patients experienced locoregional recurrence and 217 (92%) patients had distant metastasis. The distribution of relapse sites, including the frequency of intracranial metastases, did not differ significantly between molecular subgroups (*ALK* vs. *EGFR*, p=0.54; *ALK* vs. *KRAS*, p=1.00). Fourteen of the 29 (48%) patients with *ALK*-positive NSCLC developed recurrent disease during surveillance, including 2 of 10 patients (20%) with stage I NSCLC, 2 of 6 (33 %) with Stage II NSCLC, and 10 of 13 (77%) patients with stage III NSCLC. Among the 255 patients with *EGFR*-mutant NSCLC, 63 (25%) relapsed, while 158 of the 480 (33%) patients with *KRAS*-mutant NSCLC relapsed during the surveillance period.

Median RFS was 24.3 months (95% CI: 11.4–65.3) for patients with *ALK*-positive NSCLC but not reached for patients with *EGFR*-mutant NSCLC and 72.9 months (95% CI: 59.7 to undefined) for patients with *KRAS*-mutant NSCLC. There was no RFS difference between

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patients with *ALK*-positive and *KRAS*-mutant tumors when adjusted for stage (HR=1.3 ALK vs. KRAS, 95% CI: 0.8–2.1). When adjusted for stage at diagnosis, *ALK*-positive NSCLC was associated with inferior RFS compared to *EGFR*-mutant NSCLC (HR 1.8, 95% CI: 1.1–3.1). Of note, 41 (16%) patients with *EGFR*-mutant cancer received adjuvant EGFR inhibitors. A subgroup analysis was performed to determine if the difference in RFS was influenced by TKI exposure. When patients treated with adjuvant *EGFR* TKIs were excluded and stage controlled, RFS for patients with *ALK*-positive NSCLC was numerically shorter than those with *EGFR*-mutant tumors, but the trend was not statistically significant (HR=1.6, 95% CI: 0.9–2.8, p=0.104). RFS by genotype (excluding patients who received an adjuvant EGFR inhibitor) is presented in Table 2 and Figures 1A and 1B. An RFS analysis which includes patients who received an adjuvant EGFR inhibitor is presented in Supplemental Figure 1.

Overall Survival

201 (26%) patients died during follow-up, including 11 patients with *ALK*-positive, 42 patients with *EGFR*-mutant, and 148 patients with *KRAS*-mutant NSCLC. In patients with Stage I–II NSCLC, 5-year OS rates were 84% of *ALK*-positive, 88% of *EGFR*-mutant, and 72% of *KRAS*-mutant patients and OS was not significantly different (*ALK* vs *EGFR* p=0.353; *ALK* vs *KRAS* p=0.472). Among patients with Stage III NSCLC, the 5-year OS rate was 29% in the *ALK*-positive, 47% and 38% in the *EGFR*- and *KRAS*-mutant groups, respectively. There was no statistical difference in OS in Stage III (*ALK* vs *EGFR* p=0.190; *ALK* vs *KRAS* p=0.844). When patients who received adjuvant EGFR TKIs were excluded, the 5-year survival rate for *EGFR*-positive patients was 87% for stage I–II and 39% for Stage III. Table 3 and Supplemental Figures 2A and 2B depict OS of patients who did not receive adjuvant genotype-guided therapy. Supplemental Figure 3 illustrates the results of the same analysis, but includes patients who received an EGFR inhibitor in the adjuvant setting.

DISCUSSION

The diagnosis and treatment of patients with metastatic NSCLC has been revolutionized by the detection of driver alterations and development of personalized therapies targeting these alterations.[9] Although widespread implementation of molecular testing for NSCLC has been critical to characterizing these molecular subsets, the speed of drug development has confounded our ability to discern the prognostic implications of these molecular drivers. The same is not true in early-stage disease where studies of targeted therapies lag years behind approvals in advanced disease.[10] The current lack of approved adjuvant/neo-adjuvant targeted therapies offers a unique opportunity to determine whether specific molecular alterations influence the natural history of resected NSCLC. Arguably, establishing prognostic relevance may be most valuable in early- stage disease where rational design of perioperative clinical trials may lead to cures.

To date, defining the prognostic impact of molecular drivers of early-stage NSCLC has been challenging due to the relative rarity of these subsets and the redefinition of comparator arms over time as understanding of the molecular drivers of NSCLC evolved. Indeed, use of

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molecularly heterogeneous comparator arms likely obscures interpretation of findings from the previously published, early-stage ALK studies. For example, the Lungscape project, a European multi-institutional effort that analyzed prevalence and disease outcomes of resected *ALK*-positive NSCLC through study of a large biobank of lung adenocarcinomas, reported superior RFS and OS for patients with *ALK*-positive early-stage NSCLC.[3] In contrast, two separate studies observed an association between *ALK*-positivity and inferior RFS [4,6]. These latter two studies exclusively evaluated outcomes among never-smokers, whereas the comparator population in the Lungscape study was predominantly comprised of smokers. Furthermore, these studies assessed *ALK*-positive and *ROS1*-postive cancers as a single group and included a mix of genotypes in the comparator cohort. Considering that most lung cancer arises in smokers and the biology of lung cancer among never-smokers is influenced by genotype, establishing the true prognostic relevance of *ALK* status in early-stage NSCLC will ultimately depend on assessment of disease outcomes of patients with *ALK*-positive lung cancer relative to other molecularly-defined cohorts, including cohorts that include smokers.

Here, we present results from a large multi-institution study that included three molecularly-defined NSCLC subsets encompassing a spectrum of tobacco exposure. We did not observe a statistical difference when RFS of patients with resected *ALK*-positive tumors was compared to that of patients with *EGFR*- mutant NSCLC who had not received an EGFR inhibitor or patients with *KRAS*-mutant tumors. However, there were numerical differences favoring the non-ALK groups. Our findings are intriguing, but they must be interpreted within the limitations of our study, including the retrospective nature of the analysis, differences in stage distribution across oncogenic drivers, and the small number of *ALK*-positive patients studied. The frequency of relapse across molecular cohorts despite curative intent therapy highlights the importance of enrolling patients with *ALK*-positive or *EGFR*-mutant lung cancer on studies of targeted therapies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- One-third of resected *ALK*-, *KRAS*- or *EGFR*-positive lung cancer patients relapsed within 5 years.
- *ALK*-positive patients had a numerically shorter relapse-free survival than other groups.
- Relapse-free survival was not statistically different when molecular subgroups were compared.
- There was no statistical difference in overall survival across molecular groups.

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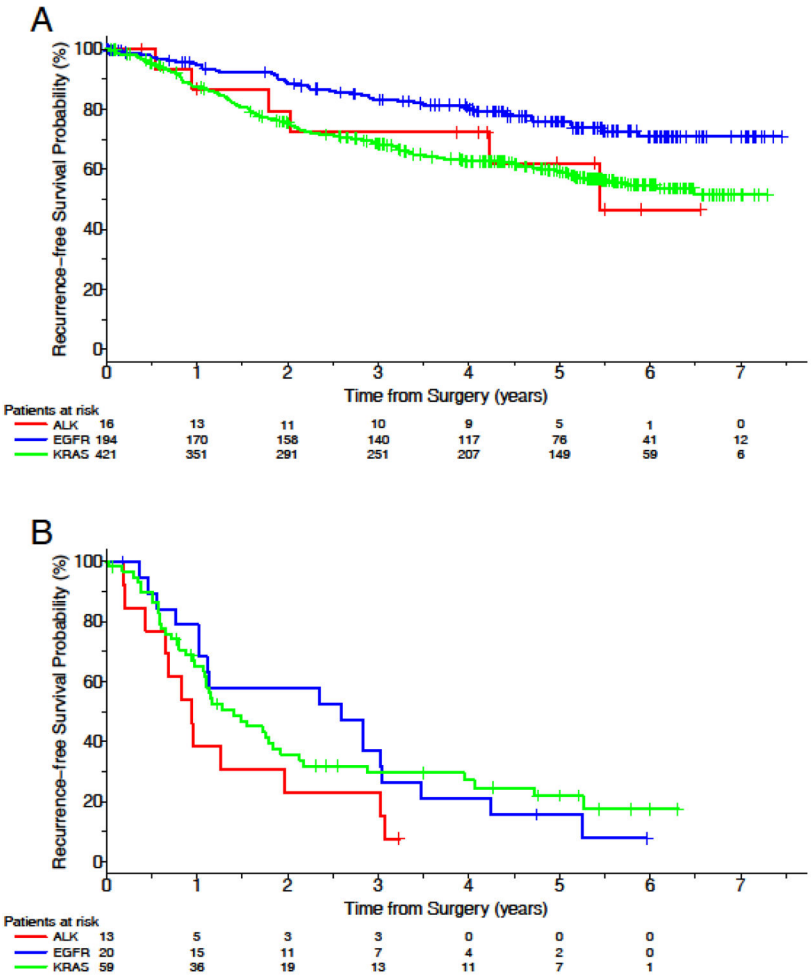

Figure 1.

Recurrence free survival by genotype when patients treated with an adjuvant EGFR tyrosine kinase inhibitor were excluded. (A) Stages I and II. (B) Stage III.

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Lung Cancer. Author manuscript; available in PMC 2019 August 01.

Table 1

Clinicopathological Characteristics and Treatment Histories

Clinical Characteristics	ALK (*n* = 29)	EGFR (*n* = 255)	KRAS (*n* = 480)	ALK vs. EGFR p-value	ALK vs. KRAS p-value
Age at Diagnosis (years)				0.002	0.001
Median	63	67	68		
Range	29–78	37–90	41–89		
Sex—number (%)				0.013	0.325
Male	13 (45)	58 (23)	171 (36)		
Female	16 (55)	197 (77)	309 (64)		
Smoking History—number (%)				0.186	<0.001
Never	17 (59)	131 (51)	23 (5)		
Light (≤10 pack years)	8 (28)	50 (20)	27 (6)		
Heavy (> 10 pack years)	4 (14)	73 (29)	430 (90)		
Unknown	0 (0)	1 (<1)	0 (0)		
Histology-number (%)				0.117 *	0.252 *
Adenocarcinoma	27 (93)	251 (98)	465 (97)		
Adenosquamous	1 (3)	3 (1)	10 (2)		
Spindle Cell	1 (3)	0 (0)	0 (0)		
Pleomorphic Carcinoma	0 (0)	1 (<1)	2 (<1)		
Not Otherwise Specified	0 (0)	0 (0)	3 (<1)		
Stage - number (%)				<0.001	<0.001
Stage I	10 (34)	194 (76)	351 (73)		
Stage II	6 (21)	25 (10)	70 (15)		
Stage III	13 (45)	36 (14)	59 (12)		
Treatment Stage I -number (%)				1.000	1.000
Surgery alone	10 (100)	189 (97)	337 (97)		
Adjuvant Chemotherapy	0 (0)	5 (3)	14 (3)		

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Clinical Characteristics	ALK (*n* = 29)	EGFR (*n* = 255)	KRAS (*n* = 480)	ALK vs. EGFR p-value	ALK vs. KRAS p-value
Treatment Stage II - number (%)				0.394	0.692
Surgery alone	2 (33)	14 (56)	31 (44)		
Adjuvant Chemotherapy	4 (67)	11 (44)	39 (56)		
Treatment Stage III - number (%)				1.000	1.000
Surgery alone	3 (23)	7 (19)	13 (22)		
Neoadjuvant Chemoradiation	6 (46)	17 (47)	26 (44)		
Neoadjuvant Chemotherapy	4 (31)	12 (33)	16 (27)		
Adjuvant Radiation	0 (0)	0 (0)	4 (7)		
EGFR TKI—number (%)					
Stage I	0 (0)	16 (8)	0 (0)		
Stage II	0 (0)	9 (36)	0 (0)		
Stage III	0 (0)	16 (44)	0 (0)		

*Adenocarcinoma versus other histologies

Note: All patients underwent surgical resection.

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Table 2

Recurrence-Free Survival (RFS) By Genotype

Molecular Driver	Median RFS Months (95% CI)	ALK vs. EGFR Hazard Ratio (95% CI)	ALK vs. KRAS Hazard Ratio (95% CI)
ALK	24.3 months (11.4 to 65.3)	1.6 0.9–2.8	1.3 0.8–2.1
EGFR *	Not reached		
KRAS	72.9 months (59.7 to not reached)		

* Patients who received EGFR tyrosine kinase inhibitors are excluded; CI: confidence interval

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Table 3

Overall Survival (OS) By Genotype

Molecular Driver	5-Year OS (%)	ALK vs. EGFR P-value	ALK vs. KRAS P-Value
Stage I & II Patients			
ALK	84	0.383	0.472
EGFR *	87		
KRAS	72		
Stage III Patients			
ALK	29	0.545	0.844
EGFR *	39		
KRAS	38		

* Patients who received EGFR tyrosine kinase inhibitors are excluded