BRIEF REPORT

Efficacy of Targeted Inhibitors in Metastatic Lung Squamous Cell Carcinoma With *EGFR* or *ALK* Alterations

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ABSTRACT

Introduction: The efficacy of targeted therapies in oncogene-driven lung adenocarcinomas (LUADs) has been well established; however, the benefit for *EGFR*-mutant or *ALK*-rearranged lung squamous cell carcinomas (LUSCs) is less known, partially owing to the rarity of the incidence.

Methods: We reviewed the database of the MD Anderson Cancer Center and identified metastatic LUSC with classic *EGFR* or *ALK* alterations.

Results: There were eight patients with *EGFR*-mutant LUSC (median age = 58 y) and six patients with *EML4-ALK* LUSC (median age = 50 y) who received tyrosine kinase inhibitors (TKIs) that were identified. Of the 14 patients, 11 (79%) were females and 12 (86%) were never smokers, similar to the demographics of *EGFR* or *ALK* LUAD. With TKI treatment, seven of eight cases of *EGFR* LUSC and four of six cases of *ALK* LUSC achieved partial response or stable disease, but the progression-free survival was 4.9 months and 2.9 months for *EGFR*-mutant and *ALK*-rearranged LUSC, respectively. In addition, we compared comutation profile of *EGFR*-mutant LUAD (The Cancer Genome Atlas, n = 46) versus LUSC (n = 19) and found that the comutation patterns are more consistent with squamous disease with a higher incidence of *PIK3CA* ($p = 0.02$) and *KRAS* or *BRAF* ($p = 0.04$) alterations.

Conclusions: *EGFR* or *ALK* alterations occur in patients with LUSC, especially never-smoker females. TKI treatments render clinical benefit in disease control, but the duration

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Drs. Lewis and Hong contributed equally to this work.

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was considerably truncated compared with those historically observed in LUAD.

Keywords: Lung squamous cell carcinoma; Targeted therapy; Tyrosine kinase inhibitor; EGFR; ALK

Introduction

Actionable genomic alterations have revolutionized the treatment paradigm for lung adenocarcinoma (LUAD). With actionable oncogenes occurring in 20% to 60% of LUAD,[1] many patients have targeted therapy as an option and therefore improved clinical outcome. Lung squamous cell carcinoma (LUSC) is the second most common disease (20%–25%) of NSCLC.[2] In comparison, actionable oncogenes in LUSC are less defined.

The incidences of genetic drivers were observed at a lower rate in LUSC, although the reported prevalence has varied across studies. In the Pan-Lung Cancer whole-exome sequencing LUSC cohort, actionable alterations in *EGFR* (0.8%), *MET* (exon 14 skipping [0.2%] or amplification [1%]), and *BRAF* (1.2%) seem to be uncommon.[3,4] A higher rate of *EGFR*-sensitizing mutations was reported in advanced LUSC tumors, including in 6% of patients with stage IIIB or IV LUSC from LUX-8, yet still significantly lower than the *EGFR* mutation incidence for LUAD.[5] The overall incidence of *ALK* fusions in LUSC is mostly limited to case reports.[6] Recently, using circulating tumor DNA (ctDNA) detection, Lam et al.[3] reported 11 of 410 (2.7%) *EGFR* mutation and 2 of 410 (0.5%) *ALK* fusion (2.4%) in LUSC.

With only sporadic cases being reported, the demographics of LUSC with *EGFR* or *ALK* alterations has not been described. Furthermore, the efficacy of targeted therapy for patients with *EGFR* or *ALK* LUSC remains unclear. In this brief report, we described the demographics and comutation profiles of 14 metastatic LUSC cases with classical *EGFR* or *ALK* alterations and responses to targeted tyrosine kinase inhibitors (TKIs).

Methods

Study Design

We reviewed the clinical and pharmacy database of patients with metastatic LUSC treated at the MD Anderson Cancer Center (MDACC) from February 2010 to December 2018 with EGFR or ALK TKIs. Patients with adenosquamous or synchronous or metachronous adenocarcinoma were excluded. The disease was confirmed by immunohistochemistry markers, including CK5/6/7, P40/P63, TTF-1, and napsin A (Table 1). Next-generation sequencing was used to evaluate *EGFR* alterations in tissue or ctDNA. *ALK* was evaluated using tissue fluorescence in situ hybridization test or next-generation sequencing–based RNA sequencing. Patients with *EGFR* exon 19 deletion (ex19del) or exon 21 L858R mutation or fusion in *ALK* treated with TKI for more than or equal to 2 months were included. Response assessment was based on Response Evaluation Criteria in Solid Tumors version 1.1. This study was conducted in accordance with the provisions of the Declaration of Helsinki and Good Clinical Practice guidelines. Institutional review boards approved the study, and as a retrospective review, no consent is required.

Molecular Landscape Comparison

In addition to the current cohort, we obtained molecular data of 11 previously published LUSC cases detected by Guardant360.[3] The cancer genomics of 46 patients with LUAD with *EGFR* ex19del or L858R were obtained from The Cancer Genome Atlas (TCGA) with an integrative analysis using cBioPortal bioinformatic tools (http://www.cbioportal.org/), as previously described.[7,8]

Results

LUSC With EGFR Mutation (Cases Number 1-8)

Eight patients with LUSC had tumors with classical *EGFR* mutations, including seven ex19del and one L858R, with six detected in tissue and two in ctDNA (Tables 1 and 2). The median age at diagnosis was 58 (range: 45–83) years. Seven patients were female, including six nonsmokers. The only male patient had a three pack-year smoking history. One patient had metastatic disease in the brain, one in the adrenal, two in the liver, five in the bone, and all had hilar or mediastinal lymph node metastases. All eight tumors had confirmed p40 positivity, and six had negative TTF1/napsin A result (Table 1).

Four patients were treated with erlotinib as first line and the other four with osimertinib, which included two as the second-line therapy after chemoimmunotherapy (cases number 6 and 8; Fig. 1*A*). The median progression-free survival (PFS) to TKIs was 4.9 (range: 3.8–7.5) months. Five patients had partial response (PR) lasting more than or equal to 4 (durations: 4.2, 4.5, 5.2, 6.3, and 7.5) months, and two had stable disease lasting 3.8 and 6.5 months, respectively. One patient treated with osimertinib as first line had disease progression at the first imaging assessment. Three of the four patients receiving erlotinib as first line acquired T790M mutation at the time of erlotinib progression and switched to osimertinib. The PFS for the second-line osimertinib was 2.0, 7.1 (censored owing to loss of follow-up), and 9.6 months. At

Table 1. IHC Markers and EGFR or ALK Detection With Comutations for Patients With LUSC

	IHC				Molecular testing		ALK
case #	CK5/6/7	P40/P63	TTF-1	Napsin A	NGS (50-146 gene panel)- Tissue	NGS (70-74 gene panel)- Blood	RNA seq (tissue or blood) or FISH
1	positive	positive	negative	NA	EGFR: p.Leu747_Ser752 delinsGln	PDGFRA:p.D173N	NA
2	NA	positive	negative	NA	EGFR:p.E746_A750del; TP53:p.E224D	EGFR:p.E746_A750del; TP53:p.E224D; ROS1:p.R1948H	negative
3	positive	positive	negative	negative	EGFR:p.L858R	negative	NA
4	positive	positive	negative	negative	EGFR:p.E746_A750del; TP53:p.V143M	NA	negative
5	positive	positive	negative	negative	NA	EGFR:p.E746_A750del; TP53:p.M246T; PIK3CA:p.H1047L	NA
6	NA	positive	NA	NA	NA	EGFR:p.A750_I759delinsPN; TP53:p.C242fs; PIK3CA:p.L755V; MYC:p.R349T	NA
7	NA	positive	NA	NA	EGFR:p.E746_A750del; TP53:p.P190L; NOTCH1:p.N253K	EGFR:p.E746_A750del; TP53:p.P190L	negative
8	NA	positive	negative	NA	EGFR:p.E746_A750del; TP53:p.L137_V143delinsP; STK11:p.Q220[a]; PIK3CA:p.H1047R	NA	negative
9	positive	positive	negative	negative	NA	negative	EML4-ALK fusion
10	NA	positive/positive	negative	NA	TP53:p.Q192[a]	TP53:p.Q192[a]	EML4-ALK fusion
11	positive	positive	negative	NA	negative	NA	EML4-ALK fusion
12	NA	NA	NA	NA	TP53:p.G154V; TSC1:p.R1097H	NA	FISH posituve
13	NA	NA	NA	NA	SMAD4:p.G419W	NA	FISH posituve
14	NA	positive	NA	NA	NA	NA	FISH posituve

[a]Truncating mutations to a stop codon.
#, number; FISH, florescence in situ hybridization; IHC, immunohistochemistry; LUSC, lung squamous cell carcinoma; NA, not available; NGS, next-generation sequencing; RNA seq, RNA sequencing.

the time of cutoff, five patients had died. Median overall survival was 16.9 (range: 8.6–27.4) months.

We evaluated the profile of co-occurring genomic alterations of *EGFR*-mutant LUSC in comparison to *EGFR*-mutant LUAD. The *EGFR*-mutant LUSC cohort included eight MDACC cases (6 with tissue sample) and 11 cases from Guardant360 in a previous publication.[3] The sample and test information for eight MDACC cases were found in Tables 1 and 2. A total of 46 *EGFR*-mutant LUAD cases were obtained from TCGA (see Methods section). Coalterations *PIK3CA* (26% versus 4%, $p = 0.02$) and *KRAS* or *BRAF* (26% versus 6%, $p = 0.04$) were more common in LUSC compared with LUAD, whereas *TP53* occurred with similar incidence (68% versus 52%, $p = 0.28$; Fig. 1*B* and C).

LUSC With EML4-ALK Fusion (Cases Numbers 9-14)

Six patients with LUSC had tumors with *EML4-ALK* rearrangement, four females and two males, all never smokers, and with a median age of 50 (range: 33–58) years. ALK TKIs (two alectinib, one brigatinib, three crizotinib) were used as first-line therapy in four patients and second-line therapy in two patients (case numbers 11 and 12; Fig. 1*A*). At data cutoff, five patients had disease progression on TKI. The median PFS of these five patients was 2.8 (range: 1.8–6.3) months. Case number 11 (PFS = 32 mo) was treated with nivolumab/ipilimumab followed by aggressive radiation/surgery to reduce tumor burden and subsequent treatment with alectinib and brigatinib. Two patients (case numbers 10 and 14) received two lines of different ALK TKIs after progression on the first TKI. The PFS during the second-line treatment was 3.8 and 1.9 months. The median overall survival was 8.3 (range: 3.2–32.1) months for *ALK*-rearranged LUSC, with three patients deceased and three alive (Fig. 1*A*).

We compared comutation profiles of seven ALK-rearranged LUSC (five from MDACC and two from Guardant360)[3] with the 28 LUAD cases from TCGA.[7–9] *TP53* mutations were common in LUSC (three of seven, 45%), but there were only five cases in LUAD (18%).

Table 2. The Clinical Characteristics of Patients

Characteristics	EGFR Mutation (n = 8)	EML4-ALK Fusion (n = 6)
Median age (range), y	58.0 (45-83)	50.0 (33-58)
Sex		
Male	1	2
Female	7	4
Smoking history		
Former	2	0
Never	6	6
Brain metastasis		
Yes	1	0
No	7	6
Bone metastasis		
Yes	5	3
No	3	3
Specimen		
Tissue	4	4
ctDNA	2	1
Tissue and ctDNA	2	1
Best response to first TKI		
PR	5	1
SD	2	3
PD	1	2
Median PFS (range), mo	4.9 (3.8-7.5)	2.9 (1.8-32.1)
Median OS (range), mo	16.9 (8.6-27.4)	8.3 (3.2-32.1)

ctDNA, circulating tumor DNA; OS, overall survival; PD, disease progression; PFS, progression-free survival; PR, partial response; SD, stable disease.

MYC amplification occurred in one case (14%) of the LUSC group and two cases (7%) of the LUAD group. Other co-occurring genomic alterations were rare in either group (Table 1).

Discussion

Here, we reviewed a cohort of LUSC with classical EGFR or ALK alterations. Median age was 58 years for *EGFR*-mutant LUSC and 50 years for *ALK*-rearranged, and most of the cases were female nonsmokers. For *EGFR*-mutant LUAD, the median age at diagnosis was 57 to 64 years, with female (62%–80%) and nonsmoker (63%–93%) predominance. For *ALK*-rearranged LUAD, the median age was 50 to 56 years, with 55% to 61% females and 62% to 65% nonsmokers.[10] Therefore, EGFR or ALK LUSC demographics are similar to those of EGFR or ALK LUAD, but distinctly different from the general LUSC group, wherein more than 80% are males and 95% are smokers.[5]

Therapeutic benefit of targeted therapy for *EGFR* or *ALK* alterations is less known for *EGFR* or *ALK* LUSC. In small cell and neuroendocrine lung cancers, it is generally thought that disease or lineage identity overrides pathway dependency, for example, SCLC with *EGFR* mutations are generally not responsive to TKI, but to platinum-etoposide chemotherapy.[11] In our LUSC case series, we found that TKIs still render some clinical benefit with disease control (PR and SD) in seven of eight *EGFR* and four of six *ALK* LUSC; however, the benefit was truncated with significantly shorter PFS compared with LUAD with the same set of alterations, *EGFR* PFS 4.9 months in LUSC compared with 10 to 19 months[12] in nonsquamous and *ALK* PFS 2.9 months in LUSC compared with 24 to 36 months[13] in nonsquamous lung cancers, in line with previous reports.[14] Interestingly, three of the four cases treated with first-generation erlotinib developed T790M at the time of progression and switched to osimertinib. Two achieved PR or stable disease and lasted more than 7 months. This result suggests that similarly to LUAD, T790M remained the predominant resistant mechanism in patients with LUSC treated with first-generation EGFR TKI and might achieve clinical benefits from subsequent osimertinib. *ALK* LUSC outcome is especially inferior compared with *ALK* LUAD, consistent with multiple previous studies that reported LUSC harboring an *EML4-ALK* rearrangement were unsuccessfully treated with ALK TKI.[15] The therapeutic effect of ALK TKI in patients with LUSC remains controversial.

There are several limitations to this study, mainly owing to small sample size and lack of comprehensive genetic profiling; therefore, all comparisons need to be interpreted with caution. The comutation profiling comparison was made by comparing this metastatic cohort before TKI treatment to a surgically resected

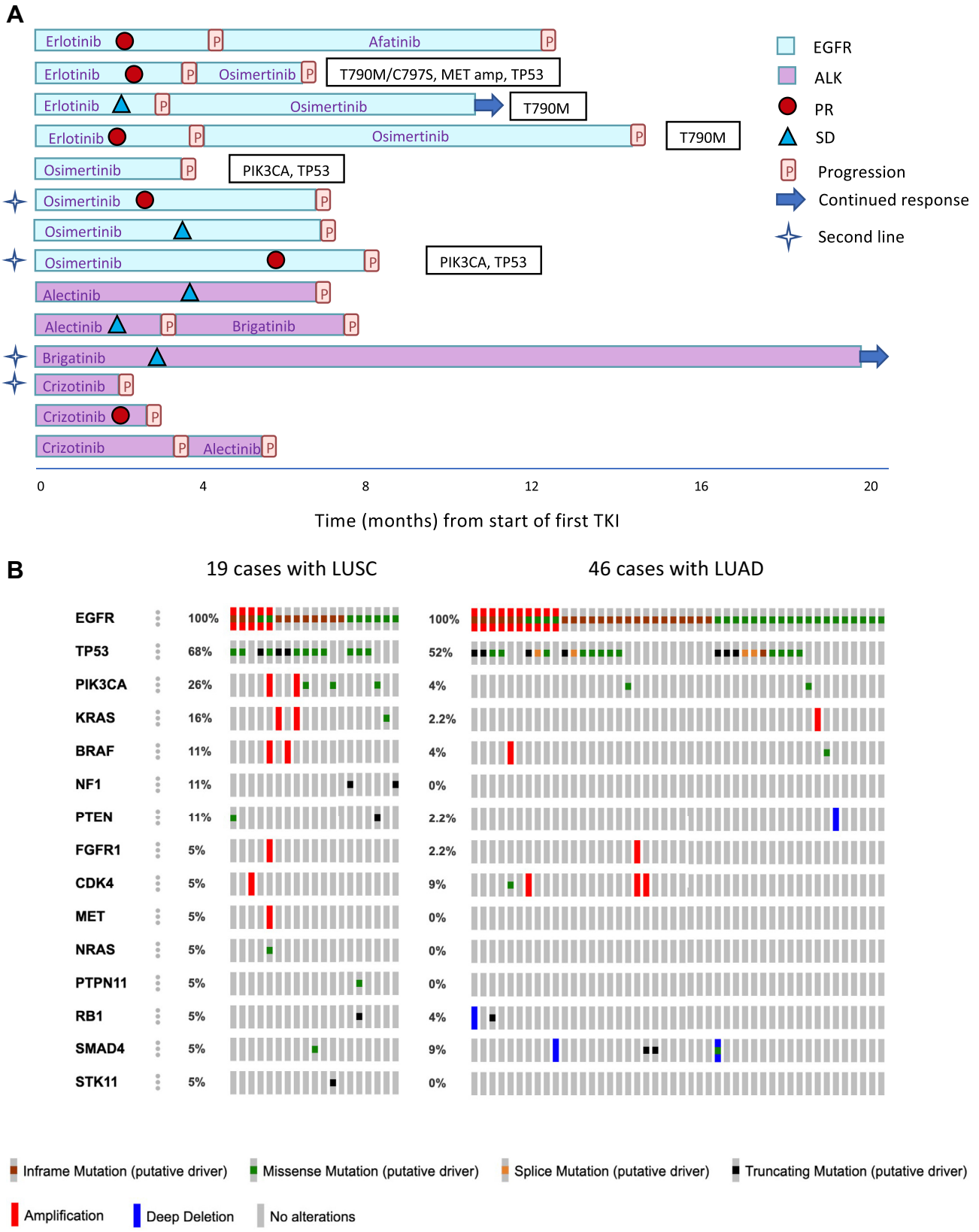

Figure 1. LUSC with EGFR/ALK alterations. (*A*) Waterfall plot of TKI responses. (*B*) Comutation plots of EGFR-mutant LUSC versus LUAD (TCGA). (*C*) Comparison of frequency of comutations in EGFR-mutant LUSC versus LUAD. LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; PR, partial response; SD, stable disease; TCGA, The Cancer Genome Atlas; TKI, tyrosine kinase inhibitor.

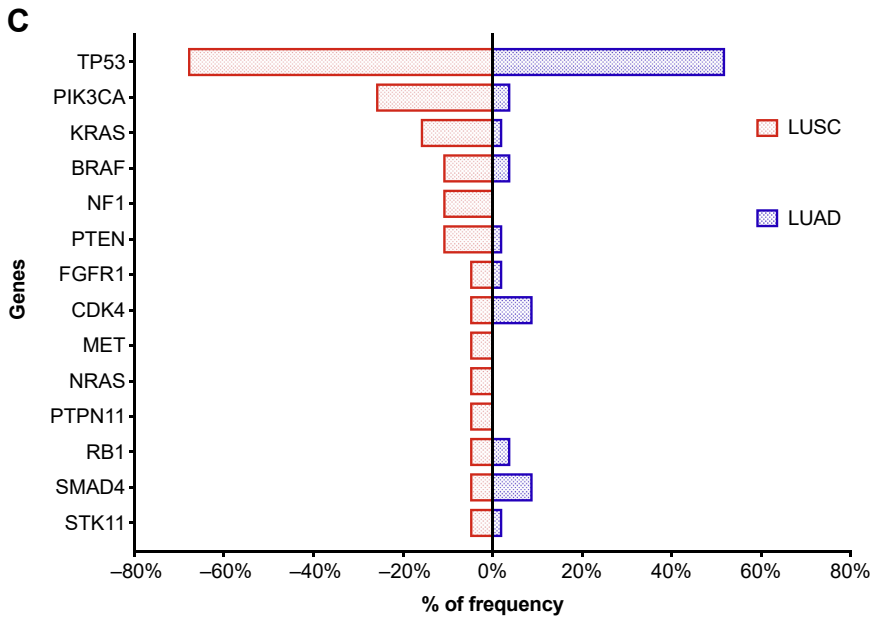

Figure 1. Continued.

cohort using clinical panels versus whole-exon sequencing results, which warrants future analysis for validation. In addition, the cohort is limited to squamous disease, and expansion to other lung cancer pathological types, such as neuroendocrine and other mixed histologies, is needed.

Our results revealed that *EGFR* or *ALK* driver alterations occur in patients with LUSC, especially nonsmoker females. TKI treatments render clinical benefit. Comprehensive genetic testing should be recommended to all patients with metastatic NSCLC, and targeted therapies should be considered an option for LUSC with *EGFR/ALK* altered.

CRediT Authorship Contribution Statement

Whitney E. Lewis, Lingzhi Hong: Study design, Data curation, Analysis, Writing.

Frank E. Mott, George Simon, Carol C. Wu, **Waree Rinsurongkawong**: Data curation.

J. Jack Lee: Study design, Data curation.

Vincent K. Lam, Jianjun Zhang, **Xiuning Le:** Supervision, Study design, Data curation, Analysis, Writing.

John V. Heymach: Supervision, Study design.

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