



# Case Report: EGFR-Positive Early-Stage Lung Adenocarcinoma Transforming to Squamous Cell Carcinoma After TKI Treatment

Jiatao Liao<sup>1,2</sup>, Yuan Li<sup>2,3</sup>, Chang Liu<sup>1,2</sup>, Qianqian Long<sup>1,2</sup> and Jialei Wang<sup>1,2\*</sup>

<sup>1</sup> Department of Medical Oncology, Fudan University Shanghai Cancer Center, Shanghai, China, <sup>2</sup> Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, China, <sup>3</sup> Department of Pathology, Fudan University Shanghai Cancer Center, Shanghai, China

## OPEN ACCESS

### Edited by:

Mantang Qiu,  
Peking University People's Hospital,  
China

### Reviewed by:

Rong Yin,  
Jiangsu Key Laboratory of Molecular  
and Translational Cancer Research,  
China

Paola Massimi,

International Centre for Genetic  
Engineering and Biotechnology, Italy

### \*Correspondence:

Jialei Wang  
luwangjialei@126.com

### Specialty section:

This article was submitted to  
Molecular and Cellular Oncology,  
a section of the journal  
Frontiers in Oncology

Received: 18 April 2021

Accepted: 24 May 2021

Published: 08 June 2021

### Citation:

Liao J, Li Y, Liu C, Long Q and Wang J  
(2021) Case Report: EGFR-Positive  
Early-Stage Lung Adenocarcinoma  
Transforming to Squamous Cell  
Carcinoma After TKI Treatment.  
*Front. Oncol.* 11:696881.  
doi: 10.3389/fonc.2021.696881

The histological transformation from epidermal growth factor receptor (EGFR)-mutated adenocarcinoma (ADC) to squamous cell carcinoma (SCC) after tyrosine kinase inhibitor (TKI) treatment is rare. We present a case of a patient who transitioned from early-stage primary lung ADC with partial squamous differentiation, *EGFR* mutation and amplification, to adrenal gland metastasis as SCC with *EGFR* amplification disappearance 115-months after surgery, during which gefitinib and local radiotherapy were utilized for the metastasis in the right femoral head and mediastinal lymph nodes. This case might indicate a possible mechanism of EGFR inhibition resistance with SCC transition and *EGFR* amplification loss from the initially well-responding ADC, especially those with SCC or partial squamous differentiation. The optimal post-progression therapy for ADC-SCC patients is challenging and further studies are needed.

**Keywords:** lung adenocarcinoma, histological transformation, resistance to gefitinib, *EGFR* mutation, *EGFR* amplification, targeted therapy

## INTRODUCTION

The development of targeted therapy has significantly advanced the treatment of non-small cell lung cancer patients. Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) have been well supported as beneficial treatments for *EGFR*-mutated lung cancer patients (1, 2).

Despite an initial favorable response to *EGFR*-TKIs, patients typically experience disease progression within 9 to 12 months (3). The reported drug resistance mechanisms include, but are not limited to acquisition of the *EGFR* T790M mutation in exon 20, *MET* amplification, *PIK3CA* mutation, *HER2* amplification, and small cell histological transformation (4, 5).

The rare phenomenon of transformation from lung adenocarcinoma (ADC) to squamous cell carcinoma (SCC) during *EGFR* inhibition treatment has also been described as a possible mechanism involving the acquired resistance to *EGFR*-TKIs (6–8). Herein, we present a new case of *EGFR*-mutant (exon 19 deletion) and *EGFR*-amplified early-stage lung ADC, in which

**Abbreviations:** AF, allele frequency; ADC, adenocarcinoma; CT, computed tomography; CN, copy number; EGFR, epidermal growth factor receptor; MRI, magnetic resonance imaging; SCC, squamous cell carcinoma; TKI, tyrosine kinase inhibitor.

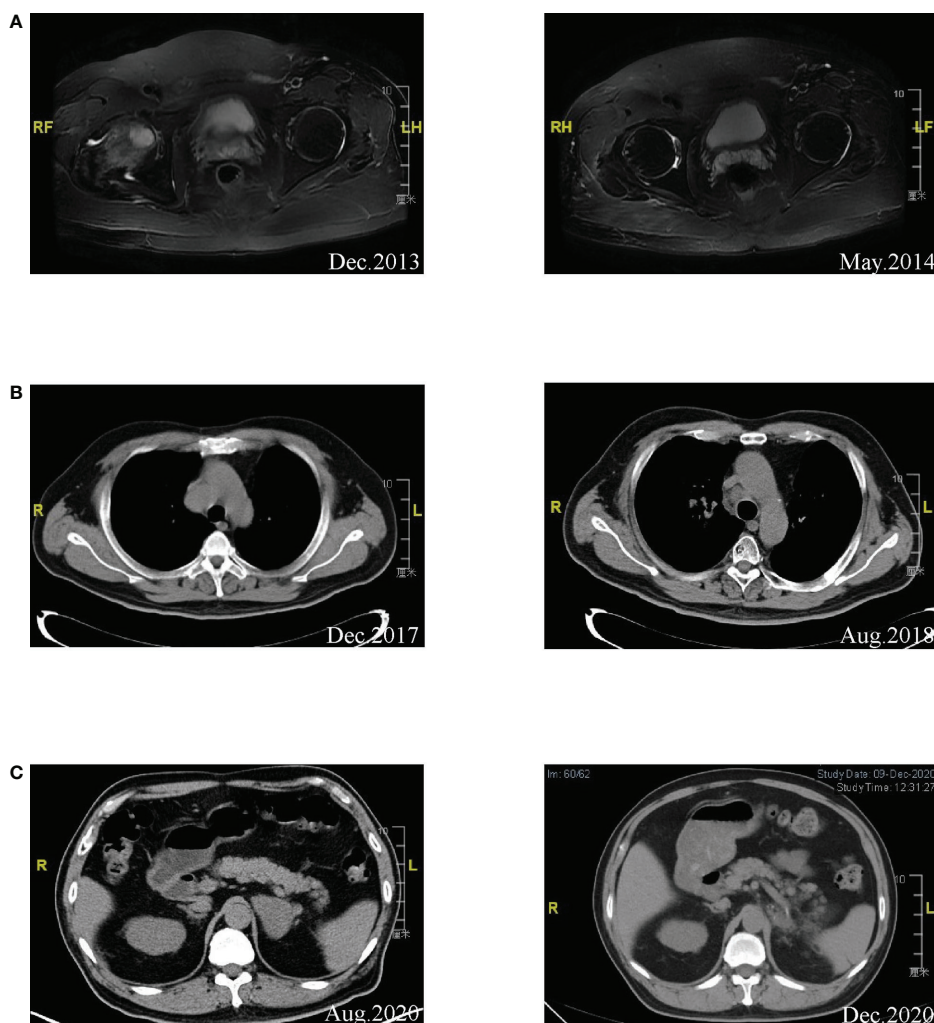
histology revealed partial squamous differentiation, undergoing transformation into metastatic SCC with the disappearance of *EGFR* amplification subsequent to a long-term standard sequential treatment involving surgery, local radiotherapy, and treatment with the first-generation *EGFR*-TKI, gefitinib.

## CASE DESCRIPTION

A 54-year-old man with no smoking history presented with persistent cough in January 2011. Thoracic computed tomography (CT) demonstrated a pulmonary left lower lobe mass. The patient underwent a left lower lobectomy with mediastinal lymph node dissection. The tumor size was 4.0 × 3.5 × 3.5 cm with no lymph node metastasis (pT2aN0M0) and

was histologically diagnosed as an adenocarcinoma. No adjuvant chemotherapy or radiotherapy was performed.

Two years after the operation, metastasis in the right femoral head was detected by magnetic resonance imaging (MRI) (**Figure 1A**). A deletion at exon 19 of the *EGFR* gene was identified by Sanger sequencing in a surgical specimen of the primary lung carcinoma. The patient started radiotherapy for the right femoral head metastasis followed by gefitinib treatment with 250 mg/day in December 2013 and showed a partial response. Mediastinal lymphadenopathy was detected by CT in December 2017 (**Figure 1B**). There was no disease progression to other sites. The patient refused endobronchial ultrasound-guided needle aspiration (EBUS-TBNA) of the mediastinal masses. Given the absence of *EGFR* T790M mutation detection in the liquid biopsy sample, he continued with gefitinib treatment and



**FIGURE 1 | (A)** Left: MRI of right femoral head indicating metastasis diagnosis. Right: A partial response was achieved after radiotherapy and gefitinib treatment. **(B)** Left: Disease progression was found in mediastinal lymph nodes by CT. Right: A partial response was achieved after continued gefitinib treatment and radiotherapy. **(C)** Left: Metastasis was detected in the left adrenal gland. Right: CT image of the patient after left adrenalectomy was performed.

received radiotherapy for the mediastinal lymph nodes in January 2018. A partial response was achieved.

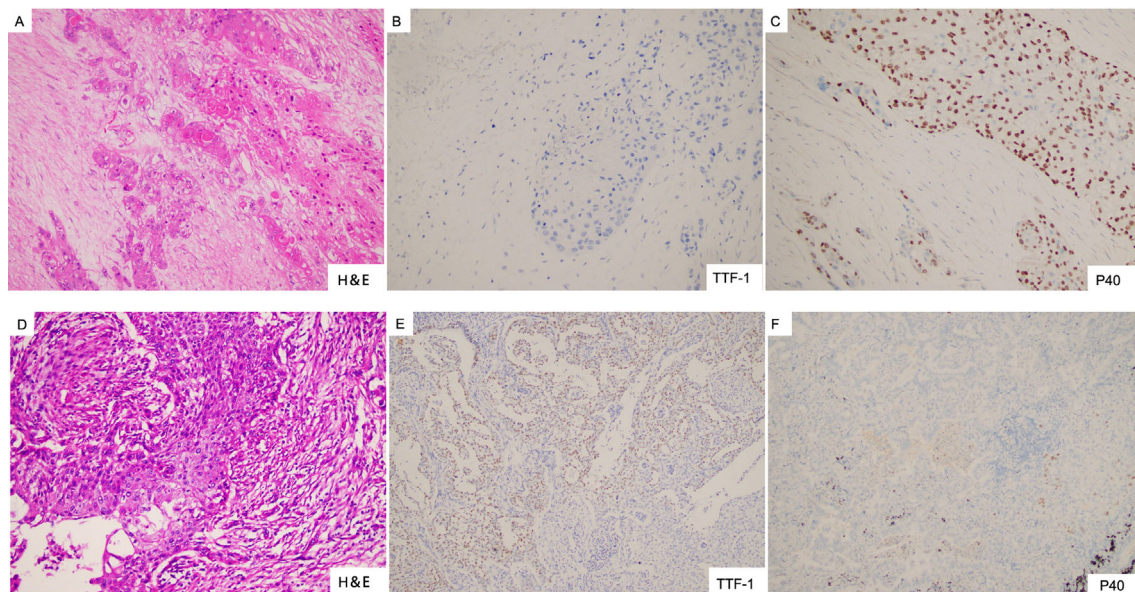
Disease progression was revealed by CT showing a metastasis in the left adrenal gland in August 2020 (**Figure 1C**). The patient then received treatment with the third-generation EGFR-TKI almonertinib at 110 mg/day in August 2020 and showed stable disease. Left adrenalectomy was performed in October 2020. Squamous cell carcinoma histology was identified from the left adrenal gland specimen by immunohistochemistry, which was TTF-1 and NapsinA negative, P40 partially positive, and CK7 positive (**Figures 2A–C**). The sample was subjected to a sequencing study using FoundationOne CDx (an FDA-approved 324-gene panel assay), and the results showed an *EGFR* exon 19 deletion (delE746\_A750, allele frequency [AF]: 26.68%). Histopathological re-examination of the surgical sample from the resected primary lung carcinoma revealed adenocarcinoma with partial squamous differentiation (less than 5%), which was partially positive for TTF-1, NapsinA,

and CK5/6, focally positive for P40, and CK7 positive (**Figures 2D–F**). Sequencing results of the initial lung specimen demonstrated the same *EGFR* 19del (delE746\_A750, AF: 80.37%) and *EGFR* amplification (copy number [CN]: 30).

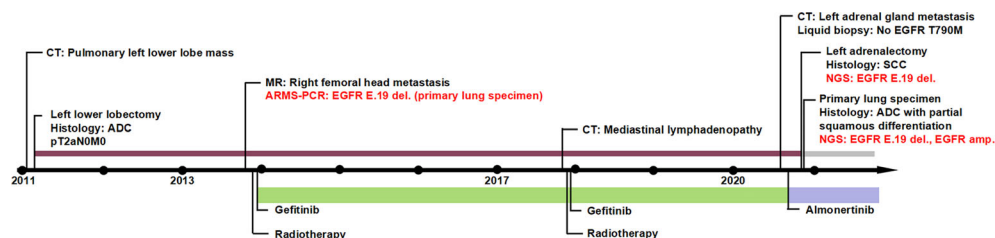
The timeline illustrating this patient's medical history and treatment is presented in **Figure 3**. The patient is currently continuing almonertinib monotherapy and the disease is stable.

## DISCUSSION

The mechanisms underlying of ADC-SCC transformation during treatment with EGFR inhibitors remain unclear. A possible explanation is that ADC and SCC co-existed in the original tumor and only the SCC component progressed following after EGFR-TKI treatment (9). In this case, pathological and immunohistochemical results revealed the transformation from lung adenocarcinoma with partial



**FIGURE 2** | (A–C) Left adrenal gland specimen showing squamous cell carcinoma with negative staining for TTF-1 and partially positive staining for P40. (D–F) Resected lung sample showing adenocarcinoma with partial squamous differentiation, expressing focally positive TTF-1 and P40.



**FIGURE 3** | Timeline of the clinical course.

squamous differentiation to metastatic SCC, which may support this assumption. There is also a possibility that pluripotent tumor stem cells acquire a divergent phenotype under the pressure of TKI (7). We considered a second primary tumor unlikely because the original *EGFR* deletion in exon 19 was maintained following the SCC transition in this patient.

Previous studies show that, *live kinase B1 (LKB1)* inactivation can promote gradual transition from lung ADC to SCC in mouse

model (10), leading to drug resistance through metabolic alteration (11). Transition of ADC-SCC with disease progression was also observed in lung cancer patients treated with chemotherapy and immunotherapy (12, 13), indicating that ADC-SCC transition might be a common drug-resistance mechanism. To better understand the link between ADC-SCC transition and *EGFR* inhibition resistance, further experimental validation is required.

**TABLE 1** | Characteristics of patients with transition to SCC from primary lung ADC after *EGFR*-TKIs treatment.

Ref	Sex/ Age	Stage	Original site		PFS	After transition to SCC			OS	Alive
			ADC genomic findings	Initial treatment		Relapsed/ metastatic site	SCC genomic findings	Subsequent therapy		
1 (6)	F/58	III	EGFR E.19 del.	Erlotinib, surgery, cisplatin/ pemetrexed, radiotherapy	11	Lung	EGFR E.19 del., E.20 T790M	NA	20	Yes
2 (14)	F/63	IV	WT	Carboplatin/pemetrexed, bevacizumab	12	Lung	EGFR E.21 L858R, E.20 T790M	NA	43	NA
3 (15)	F/51	IV	EGFR E.19 del.	Gefitinib, surgery	10	Lung	EGFR E.19 del.	Gemcitabine/ cisplatin	10	Yes
4 (15)	F/61	IV	EGFR E.21 L858R	Gefitinib	12	Pleura	EGFR E.21 L858R	Erlotinib	24	No
5 (16)	F/63	IV	EGFR E.21 L858R	Erlotinib	5	Lung	EGFR E.21 L858R, PIK3CA mut.	Gefitinib, carboplatin/ gemcitabine	14	No
6 (7)	F/66	IV	EGFR E.19 del.	Carboplatin/pemetrexed	4	Lung	EGFR E.19 del.	NA	12	No
7 (17)	F/48	III	EGFR E.19 del.	Adjuvant chemotherapy	NA	Lung	EGFR E.19 del.	NA	30	No
8 (17)	F/64	IV	EGFR E.21 L858R, E.20 T790M	Gefitinib	NA	Lung	EGFR E.21 L858R, E.20 T790M	Rociletinib	NA	Yes
9 (18)	F/74	IV	EGFR E.21 L858R	Gefitinib	9	Lung	EGFR E.21 L858R, E.20 T790M	Carboplatin/ vinorelbine	21	Yes
10 (18)	F/79	IV	EGFR E.19 del.	Gefitinib	17	Lung	EGFR E.19 del., E.20 T790M	Gefitinib	26	Yes
11 (19)	F/44	IV	EGFR E.19 del.	Afatinib, radiotherapy, denosumab	18	Lung	EGFR E.19 del., E.20 T790M	Osimertinib, radiotherapy	21	Yes
12 (20)	F/67	IV	EGFR E.19 del.	Afatinib	6	Cervical lymph node	EGFR E.19 del., PIK3CA mut.	Afatinib, platinum/ vinorelbine	10	Yes
13 (21)	F/43	IV	EGFR E.21 L858R	Gefitinib, radiotherapy	8	Lung	EGFR E.21 L858R, E.20 S768I	Gefitinib	11	No
14 (22)	M/40	I	EGFR E.19 del.	Surgery, vinorelbine/cisplatin	48	scalp	EGFR E.19 del., E.20 T790M	NA	72	NA
15 (23)	M/68	I	EGFR E.21 L858R	Surgery, tegafur/uracil	48	liver	EGFR E.21 L858R, E.20 T790M	Osimertinib	77	No
16 (24)	F/52	IV	EGFR E.19 del.	Erlotinib, bevacizumab	12	muscle	EGFR E.19 del.	Docetaxel, radiotherapy, afatinib	29	NA
17 (25)	M/62	I	EGFR E.21 L858R	Surgery, tegafur/uracil	6	Pleura	EGFR E.21 L858R	Cisplatin/ pemetrexed	16	No
18 (26)	F/67	IV	EGFR E.21 L858R, E.20 T790M	Gefitinib	58	Lung	EGFR E.21 L858R	Carboplatin/ gemcitabine	70	No
19 (27)	F/56	III	EGFR E.19 del.	Surgery, platinum doublet, gefitinib	72	Lung	EGFR E.19 del., E.20 T790M	Osimertinib, surgery	114	No
20 (28)	M/61	IV	EGFR E.19 ins.	Erlotinib	28	Lung	EGFR E.20 T790M, PTEN mut.	Osimertinib, pembrolizumab, S-1	58	No
21 (28)	M/72	IV	EGFR E.21 L858R	Erlotinib	9	Lung	EGFR E.21 L858R, E.20 T790M, PTEN mut. TP53 mut.	Osimertinib, pembrolizumab	31	No
22	M/54	I	EGFR E.19 del., EGFR amp.	Surgery	24	Adrenal gland	EGFR E.19 del.	Almonertinib, surgery	123	Yes

ADC, adenocarcinoma; Alive, alive at the last follow-up; *EGFR*-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor; NA, not available; OS, overall survival from ADC diagnosis; PFS, progression-free survival from initial treatment; SCC, squamous cell carcinoma.

The simultaneous occurrence of ADC-SCC transformation and *EGFR* inhibition resistance is rare. To date, there have been only 22 reported cases including our patient, and their characteristics are summarized in **Table 1**. Based on the available information, most patients described were female (72.7%) and the median age was 62 years (range, 40 to 79 years). In most cases, the histological transition was found at the lung recurrence site. This case is unique to present the ADC-SCC transition in the adrenal gland metastasis, which has never been reported before.

According to **Table 1**, approximately half of the patients developed *EGFR* T790M as an acquired resistance mechanism to *EGFR*-TKI therapy. Other genomic alterations included the acquired mutations in *EGFR* S768I, *PIK3CA*, *PTEN*, *TP53*. We describe the first reported histologic evolution of ADC to SCC combined with the disappearance of *EGFR* amplification.

In this case, sequencing analysis of the primary lung carcinoma demonstrated *EGFR* deletion in exon 19 (AF: 80.37%) and *EGFR* amplification (CN: 30). There is evidence indicating that lung ADC patients with higher *EGFR* mutation abundance benefit more from *EGFR*-TKIs (29). Further, high *EGFR* copy number has been associated with better clinical outcomes in *EGFR*-mutant patients treated with *EGFR*-TKI (30, 31). Studies have shown that *EGFR* amplifications usually impact mutated but not wild-type alleles (31), which is likely to increase *EGFR* mutation abundance and render cancer cells more sensitive to *EGFR* inhibition. These may explain why the effectiveness of gefitinib and local radiotherapy was sustained for up to 48 months for the first metastasis in the right femoral head, and up to 32 months for the second metastasis in the mediastinal lymph nodes.

A limitation of this report was that no biopsy of the lesions was performed for the first and second metastases. Therefore, we cannot exclude the assumption that ADC-SCC transition had already occurred before the detection of the adrenal gland metastasis.

*EGFR*-mutated patients resistant to TKIs with a changed phenotype to SCC show poor prognosis with a median overall survival of only 3.5 months (26). The management of transformed SCC after TKI resistance is controversial. According to **Table 1**, selected treatment strategies include combining chemotherapy or radiotherapy, surgery, third-generation TKI, and immunotherapy. To date, this patient has

been treated with almonertinib for 8 months with stable disease. Further studies in *EGFR*-mutant patients with TKI resistance and ADC-SCC transformation are needed to specify the underlying mechanisms and to optimize the individualized post-progression therapy.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

## ETHICS STATEMENT

Ethical review and approval were not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

## AUTHOR CONTRIBUTIONS

JW and JL designed the study drafted the manuscript. YL and CL collected and analyzed the patient data. QL and JL contributed to the literature research. JW reviewed and edited the manuscript. All authors contributed to the article and approved the submitted version.

## FUNDING

This study was sponsored by the Natural Science Foundation of Shanghai (grant number: 19ZR1410400).

## ACKNOWLEDGMENTS

We thank Lifeng Wang (Dian Diagnostics) for critical but constructive comments on this paper.

## REFERENCES

- Lynch TJ, Bell DW, Sordella R, Gurubhagavatula S, Okimoto RA, Brannigan BW, et al. Activating Mutations in the Epidermal Growth Factor Receptor Underlying Responsiveness of Non-Small-Cell Lung Cancer to Gefitinib. *New Engl J Med* (2004) 350(21):2129–39. doi: 10.1056/NEJMoa040938
- Shepherd FA, Rodrigues Pereira J, Ciuleanu T, Tan EH, Hirsh V, Thongprasert S, et al. Erlotinib in Previously Treated Non-Small-Cell Lung Cancer. *New Engl J Med* (2005) 353(2):123–32. doi: 10.1056/NEJMoa050753
- Riely GJ, Yu HA. Egfr: The Paradigm of an Oncogene-Driven Lung Cancer. *Clin Cancer Res an Off J Am Assoc Cancer Res* (2015) 21(10):2221–6. doi: 10.1158/1078-0432.Ccr-14-3154
- Sequist LV, Waltman BA, Dias-Santagata D, Digumarthy S, Turke AB, Fidias P, et al. Genotypic and Histological Evolution of Lung Cancers Acquiring Resistance to *EGFR* Inhibitors. *Sci Trans Med* (2011) 3(75):75ra26. doi: 10.1126/scitranslmed.3002003
- Yu HA, Arcila ME, Rekhtman N, Sima CS, Zakowski MF, Pao W, et al. Analysis of Tumor Specimens At the Time of Acquired Resistance to *EGFR*-TKI Therapy in 155 Patients With *EGFR*-Mutant Lung Cancers. *Clin Cancer Res an Off J Am Assoc Cancer Res* (2013) 19(8):2240–7. doi: 10.1158/1078-0432.Ccr-12-2246
- Scher KS, Saldivar JS, Fishbein M, Marchevsky A, Reckamp KL. *EGFR*-Mutated Lung Cancer With T790M-Acquired Resistance in the Brain and Histologic Transformation in the Lung. *J Natl Compr Cancer Netw JNCCN* (2013) 11(9):1040–4. doi: 10.6004/jnccn.2013.0126
- Levin PA, Mayer M, Hoskin S, Sailors J, Oliver DH, Gerber DE. Histologic Transformation From Adenocarcinoma to Squamous Cell Carcinoma as a Mechanism of Resistance to *EGFR* Inhibition. *J Thorac Oncol* (2015) 10(9):e86–e8. doi: 10.1097/JTO.0000000000000571

8. Soria JC, Felip E, Cobo M, Lu S, Syrigos K, Lee KH, et al. Pathological Transition as the Arising Mechanism For Drug Resistance In Lung Cancer. *Cancer Commun* (2015) 16(8):897–907. doi: 10.1016/s1470-2045(15)00006-6
9. Hou S, Zhou S, Qin Z, Yang L, Han X, Yao S, et al. Evidence, Mechanism, and Clinical Relevance of the Transdifferentiation From Lung Adenocarcinoma to Squamous Cell Carcinoma. *Am J Pathol* (2017) 187(5):954–62. doi: 10.1016/j.ajpath.2017.01.009
10. Han X, Li F, Fang Z, Gao Y, Li F, Fang R, et al. Transdifferentiation of Lung Adenocarcinoma in Mice With Lkb1 Deficiency to Squamous Cell Carcinoma. *Nat Commun* (2014) 5:3261. doi: 10.1038/ncomms4261
11. Li F, Han X, Li F, Wang R, Wang H, Gao Y, et al. Lkb1 Inactivation Elicits a Redox Imbalance to Modulate Non-Small Cell Lung Cancer Plasticity and Therapeutic Response. *Cancer Cell* (2015) 27(5):698–711. doi: 10.1016/j.ccell.2015.04.001
12. Le T, Sailors J, Oliver DH, Mayer M, Hoskin S, Gerber DE. Histologic Transformation of EGFR Mutant Lung Adenocarcinoma Without Exposure to EGFR Inhibition. *Lung Cancer* (2017) 105:14–6. doi: 10.1016/j.lungcan.2017.01.005
13. Hsu CL, Chen KY, Kuo SW, Chang YL. Histologic Transformation in a Patient With Lung Cancer Treated With Chemotherapy and Pembrolizumab. *J Thorac Oncol* (2017) 12(6):e75–e6. doi: 10.1016/j.jtho.2017.02.006
14. Bugano DDG, Kalhor N, Zhang J, Neskey M, William WN. Squamous-Cell Transformation in A Patient With Lung Adenocarcinoma Receiving Erlotinib: Co-occurrence With T790M Mutation. *Cancer Treat Commun* (2015) 4:34–6. doi: 10.1016/j.ctrc.2015.03.007
15. Hsieh MS, Jhuang JY, Hua SF, Chou YH. Histologic Evolution From Adenocarcinoma to Squamous Cell Carcinoma After Gefitinib Treatment. *Ann Thoracic Surg* (2015) 99(1):316–9. doi: 10.1016/j.athoracsur.2014.02.075
16. Kuiper JL, Ronden MI, Becker A, Heideman DA, van Hengel P, Ylstra B, et al. Transformation to a Squamous Cell Carcinoma Phenotype of an EGFR-Mutated NSCLC Patient After Treatment With An EGFR-tyrosine Kinase Inhibitor. *J Clin Pathol* (2015) 68(4):320–1. doi: 10.1136/jclinpath-2015-202866
17. Haratani K, Hayashi H, Watanabe S, Kaneda H, Yoshida T, Takeda M, et al. Two Cases of EGFR Mutation-Positive Lung Adenocarcinoma That Transformed Into Squamous Cell Carcinoma: Successful Treatment of One Case With Rociletinib. *Ann Oncol* (2016) 27(1):200–2. doi: 10.1093/annonc/mdv495
18. Jukna A, Montanari G, Mengoli MC, Cavazza A, Covi M, Barbieri F, et al. Squamous Cell Carcinoma “Transformation” Concurrent With Secondary T790m Mutation in Resistant Egrf-Mutated Adenocarcinomas. *J Thorac Oncol* (2016) 11(4):e49–51. doi: 10.1016/j.jtho.2015.12.096
19. Bruno R, Proietti A, Ali G, Puppo G, Ribecchini A, Chella A, et al. Squamous Cell Transformation and EGFR T790M Mutation as Acquired Resistance Mechanisms in a Patient With Lung Adenocarcinoma Treated With A Tyrosine Kinase Inhibitor: A Case Report. *Oncol Lett* (2017) 14(5):5947–51. doi: 10.3892/ol.2017.6913
20. Clery E, Pisapia P, Feliciano S, Vigliar E, Marano A, De Luca C, et al. There is Still A Role for Cytology in the ‘Liquid Biopsy’ Era. A Lesson From a TKI-Treated Patient Showing Adenocarcinoma to Squamous Cell Carcinoma Transition During Disease Progression. *J Clin Pathol* (2017) 70(9):798–802. doi: 10.1136/jclinpath-2017-204370
21. Longo L, Mengoli MC, Bertolini F, Bettelli S, Manfredini S, Rossi G. Synchronous Occurrence of Squamous-Cell Carcinoma “Transformation” and EGFR Exon 20 S768I Mutation as a Novel Mechanism of Resistance in EGFR-Mutated Lung Adenocarcinoma. *Lung Cancer* (2017) 103:24–6. doi: 10.1016/j.lungcan.2016.11.012
22. Park HK, Seo Y, Choi YL, Ahn MJ, Han J. Metastatic Squamous Cell Carcinoma From Lung Adenocarcinoma After Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Therapy. *J Pathol Trans Med* (2017) 51(4):441–3. doi: 10.4132/jptm.2016.10.18
23. Izumi H, Yamasaki A, Ueda Y, Sumikawa T, Maeta H, Nakamoto S, et al. Squamous Cell Carcinoma Transformation From EGFR-Mutated Lung Adenocarcinoma: A Case Report and Literature Review. *Clin Lung Cancer* (2018) 19(1):e63–e6. doi: 10.1016/j.clcc.2017.10.005
24. Sato M, Matsui A, Shimoyama Y, Omote N, Morise M, Hase T, et al. An EGFR-Mutated Lung Adenocarcinoma Undergoing Squamous Cell Carcinoma Transformation Exhibited A Durable Response to Afatinib. *Internal Med (Tokyo Japan)* (2018) 57(23):3429–32. doi: 10.2169/INTERNALMEDICINE.0999-18
25. Shinohara S, Ichiki Y, Fukuichi Y, Honda Y, Kanayama M, Taira A, et al. Squamous Cell Carcinoma Transformation From Adenocarcinoma as An Acquired Resistance After the EGFR TKI Therapy in (EGFR-Mutated) Non-Small Cell Lung Cancer. *J Thorac Dis* (2018) 10(7):E526–E31. doi: 10.21037/jtd.2018.06.83
26. Roca E, Pozzari M, Vermi W, Tovazzi V, Baggi A, Amoroso V, et al. Outcome of EGFR-Mutated Adenocarcinoma NSCLC Patients With Changed Phenotype to Squamous Cell Carcinoma After Tyrosine Kinase Inhibitors: A Pooled Analysis With an Additional Case. *Lung Cancer* (2019) 127:12–8. doi: 10.1016/j.lungcan.2018.11.016
27. Haruki T, Nakanishi A, Matsui S, Kidokoro Y, Kubouchi Y, Takagi Y, et al. Transformation From Adenocarcinoma to Squamous Cell Carcinoma Associated With Long-Term Administration of EGFR-Tkis. *Mol Clin Oncol* (2020) 13(6):82. doi: 10.3892/mco.2020.2152
28. Uruga H, Fujii T, Nakamura N, Moriguchi S, Kishi K, Takaya H. Squamous Cell Transformation as A Mechanism of Acquired Resistance to Tyrosine Kinase Inhibitor in EGFR-mutated Lung Adenocarcinoma: A Report of Two Cases. *Respirol Case Rep* (2020) 8(2):e00521. doi: 10.1002/rcr2.521
29. Zhou Q, Zhang XC, Chen ZH, Yin XL, Yang JJ, Xu CR, et al. Relative Abundance of EGFR Mutations Predicts Benefit From Gefitinib Treatment for Advanced Non-Small-Cell Lung Cancer. *J Clin Oncol Off J Am Soc Clin Oncol* (2011) 29(24):3316–21. doi: 10.1200/jco.2010.33.3757
30. Ruiz-Patino A, Castro CD, Ricaurte LM, Cardona AF, Rojas L, Zatarain-Barron ZL, et al. Egrf Amplification and Sensitizing Mutations Correlate With Survival in Lung Adenocarcinoma Patients Treated With Erlotinib (Mutp-Clicap). *Target Oncol* (2018) 13(5):621–9. doi: 10.1007/s11523-018-0594-x
31. Shan L, Wang Z, Guo L, Sun H, Qiu T, Ling Y, et al. Concurrence of EGFR Amplification and Sensitizing Mutations Indicate A Better Survival Benefit From EGFR-TKI Therapy in Lung Adenocarcinoma Patients. *Lung Cancer* (2015) 89(3):337–42. doi: 10.1016/j.lungcan.2015.06.008

**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2021 Liao, Li, Liu, Long and Wang. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.