Editorial

The emerging landscape of EFGR tyrosine kinase inhibitors in lung adenocarcinoma—successes and challenges

Eziafa I. Oduah[1,2], Chung-Shien Lee[3,4], Nagarashee Seetharamu[4]

[1]Division of Hematology and Oncology, Department of Internal Medicine, Virginia Commonwealth University School of Medicine, Richmond, VA, USA; [2]Massey Cancer Center, Richmond, VA, USA; [3]Department of Clinical Health Professions, St. John's University, College of Pharmacy and Health Sciences, Queens, NY, USA; [4]Division of Medical Oncology and Hematology, Northwell Health Cancer Institute, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Lake Success, NY, USA

Correspondence to: Nagarashee Seetharamu. Division of Medical Oncology and Hematology, Northwell Health Cancer Institute, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Lake Success, NY, USA. Email: Nseetharamu@northwell.edu.

Comment on: Du W, Zhao Y, Xuan Y, *et al.* Different efficacy in the non-small cell lung cancer patient with bilateral synchronous lesions treated with neoadjuvant gefitinib therapy: a case report. J Thorac Dis 2020;12:1582-7.

Song Y, Jia Z, Wang Y, *et al.* Potential treatment strategy for the rare osimertinib resistant mutation EGFR L718Q. J Thorac Dis 2020;12:2771-80.

Zheng Y, Zhou M, Arulananda S, *et al.* Management of non-small cell lung cancer with resistance to epidermal growth factor receptor tyrosine kinase inhibitor: case discussion. J Thorac Dis 2020;12:159-64.

Dai J, Greiffenstein P, Petrella F, *et al.* Treatment of a lung lobectomy patient with severe post-surgical infection in the anterior thoracic wall by multiple debridement and drainage procedures: a case report. J Thorac Dis 2020;12:7481-7.

Wang G, Lin Y, Zheng L, *et al.* A new method for accurately localizing and resecting pulmonary nodules. J Thorac Dis 2020;12:4973-84.

Jia Z, Wang Y, Cao L, *et al.* First-line treatment selection with organoids of an EGFRm + TP53m stage IA1 patient with early metastatic recurrence after radical surgery and follow-up. J Thorac Dis 2020;12:3764-73.

Zang J, Horinouchi H, Hanaoka J, *et al.* The role of salvage surgery in the treatment of a gefitinib-resistant non-small cell lung cancer patient: a case report. J Thorac Dis 2021;13:4554-9.

Submitted Apr 01, 2022. Accepted for publication Apr 20, 2022.
doi: 10.21037/jtd-22-432
View this article at: https://dx.doi.org/10.21037/jtd-22-432

Epidermal growth factor receptor (EGFR) is a member of the erbB tyrosine kinase receptor family found to be mutated and/or overexpressed lung adenocarcinoma (LADC). Mutations in *EGFR* result in activation of the MAPK pathway leading to increases in cell proliferation and survival (1). *EGFR* mutations are present in about 15 percent of LADCs and are most prevalent in Asian populations, women, never- or previous light smokers (2). *EGFR* tyrosine kinase inhibitors (TKIs) have emerged as a successful class of targeted therapeutics in LADC and have revolutionized the management of patients whose tumors harbor a mutation in the *EGFR* gene locus.

In 2003, gefitinib became the first EGFR TKI to receive FDA approval for use in the United States in the post-platinum setting irrespective or *EGFR* mutation status (3). Multiple subsequent trials demonstrated superiority in progression free survival (PFS) over platinum-doublet in the first line in patients with *EGFR* mutated LADC, moving this class of targeted therapeutics to the frontline for these patients (4-7). Since the initial studies and approvals of the first-generation EGFR TKIs, our knowledge of this class of antineoplastics and their survival implications in LADC has grown exponentially. A multitude of second, third and fourth generation EGFR TKIs have since been developed and are in clinical use or being evaluated in clinical trials in the United States and across the globe (*Table 1*).

Globally, the current treatment paradigm for *EGFR* mutant LADC incorporates the use of either first, second or third generation TKIs in the first line setting for advanced metastatic disease. However, in the United States, the 3rd generation osimertinib is the preferred first line agent based on the results of the FLAURA study that showed overall survival of 39 months in osimertinib treated group compared to 32 months in the erlotinib and gefitinib groups

Table 1 EGFR TKIs in clinical use in the United States (3,8)

Name	Indications	Year of approval
First generation		
Gefitinib	Second line for advanced or metastatic NSCLC (withdrawn)	2003
	First line in metastatic NSCLC with exon 19 (del) or exon 21 (L858R) mutations	2015
Erlotinib	First line and after progression on platinum chemotherapy for metastatic NSCLC with exon 19 (del) or exon 21 (L858R) mutations	2004
	Maintenance therapy in locally advanced metastatic disease	2010
Second generation		
Afatinib	First line in metastatic disease harboring nonresistant *EGFR* mutations	2013
	Metastatic squamous NSCLC after progression on platinum-based therapy	
Dacomitinib	First-line therapy for metastatic NSCLC with EGFR exon 19 deletion or exon 21 L858R substitution mutations	2018
Third generation		
Osimertinib	Metastatic NSCLC with EGFR T790M who have progressed on, or after EGFR TKI therapy	2015
	First line in *EGFR* mutant advanced or metastatic disease	2018

EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; NSCLC, non-small cell lung cancer.

[hazard ratio (HR) =0.80, 95% confidence interval (CI), 0.64 to 1.00] (9). The PFS was also superior with osimertinib at 19 months compared to 10 months with erlotinib and gefitinib [HR =0.46; 95% CI, 0.37 to 0.57] (10). The case report by Jia *et al.* serves as a good validation of the superiority of osimertinib in the first line setting for metastatic LADC through *in vitro* sensitivity testing (11). The authors report the case of a 66-year-old male who had recurrent LADC with metastatic disease three years after curative surgery for early-stage disease. Pathology of a biopsied lesion confirmed the presence of *EGFR* L858R and *TP53* R110L mutations. Using patient derived organoids in a personalized approach, the efficacy of five EGFR TKIs including osimertinib, afatinib, erlotinib, gefitinib and icontinib were compared. Osimertinib demonstrated superiority over all other TKIs, reaffirming the results of the FLAURA trial. The patient was then treated with osimertinib and enjoyed a PFS of about 9 months. The relatively shorter PFS in this patient is likely due to concomitant *TP53* mutation, which is known to confer a poorer prognosis when co-mutated with *EGFR* (12).

The differences in global practice in relation to EGFR TKIs is in part attributable to local availability, or lack thereof, of these TKIs which likely affects recommended practices. This is reflected in the case report by Song *et al.* in which a patient with known *EGFR* mutation was subjected to an initial 4 cycles of platinum doublet therapy due to local unavailability of TKI (13). This is also underscored in the case report by Zheng *et al.* in which another patient with recurrent metastatic LADC with brain metastases was found on biopsy to harbor *EGFR* L858R mutation (14). She was started on gefitinib with subsequent progression of the brain metastasis after a year of therapy. The authors report that the patient declined repeat biopsy of the pulmonary or brain lesions and therefore could not confirm the presence of T790M mutation. This led to initiation of second line anlotinib, a non-EGFR multitargeting TKI, rather than osimertinib since the latter could only be prescribed at this practice if there was a documented T790M mutation. While a blood-based next generation sequencing (NGS) might be helpful in assessing for resistance mechanisms in the United States today, the technology may not have been available at the patient's treating institution. Anlotinib was discontinued a month later due to intolerable side effects and osimertinib was commenced after the patient consented to biopsy with subsequent confirmation of T790M. It is important to note that among all approved EGFR TKIs, osimertinib is the only agent with activity in T790M mutated LADC and the only one that has optimal CNS penetration (9). Therefore, the treating physicians could have used that argument to support initiation of osimertinib in the presence of a brain metastasis. In another case report

Table 2 Mechanisms of acquired osimertinib resistance (18-21)

On target
EGFR mutations: C797S, L718Q, G724S, C79X, L792X, G769X, S768I, G724S, G796S, V834L exon 20 insertion
EGFR amplification
Off target
MET amplification
HER2 mutation/amplification
PIK3CA mutation/amplification
KRAS mutation/amplification
PTEN mutation
Cell cycle gene alterations: CCND1, CCND2, CDKN2A, CDK6, CCNE1
Small cell transformation
Squamous translocation

EGFR, epidermal growth factor receptor.

by Zang *et al.*, the patient with recurrent metastatic LADC harboring *EGFR* L858R mutation was initially treated with gefitinib. The patient had a clear progression disease at 27 months with the presence of T790M gatekeeper mutation. Although treatment change was warranted, the patient was continued on gefitinib for an additional 10 months due to unavailability of osimertinib in China at that time. Unfortunately, this patient developed progressive disease occurred 12 months later with brain, bone and liver metastases and eventually died from multi-organ dysfunction nine months later (15).

All three cases reported by Song *et al.*, Zheng *et al.* and Zang *et al.*, not only reflect the challenge related to availability of EGFR TKIs but also highlight an even greater challenge—the emergence of resistance to this group of antineoplastics. Despite initial responses to EGFR TKI therapy, most patients will progress due to acquisition of resistant mutations. Undoubtedly, the most common mechanism of acquired resistance to first- and second-generation EGFR TKIs is the appearance of T790M gatekeeper mutation (approximately 50%). The T790M mutation is sensitive to osimertinib, therefore patients who acquire this mutation while on first or second generation TKIs are eligible for second line osimertinib with additional PFS of about 9–13 months (10,16,17). However, most patients will also eventually develop resistance to osimertinib. The most frequent resistance mechanisms for osimertinib are summarized in *Table 2* (18-21). In the case reported by Song *et al.* (13), after the initial 4 cycles of chemotherapy, the patient was started on icotinib on which he acquired the T790M resistance mutation after 9 months of treatment. The patient was appropriately transitioned to osimertinib, however on imaging studies 4 weeks later was found to have progressive disease. Although it was too early to assess response to osimertinib at 4 weeks, NGS of a wedge resection of a metastatic pulmonary lesion showed the presence of L858R, L718Q and *EGFR* amplification with a copy number of 11.54, a genomic profile associated with resistance to osimertinib. The *EGFR* T790M mutation was negative in this resection specimen, which is likely due to suppression by Osimertinib and/or tumor heterogeneity. As per the authors, the patient was subjected to a second course of 4 cycles of platinum doublet therapy to 'clear' the composition of the tumor after which he was rechallenged with osimertinib with which he enjoyed a PFS of 4.7 months. At this point, another tumor biopsy demonstrated another well-characterized osimertinib-resistant mutation, *EGFR* C797S, which occurs with a frequency of 0.60%. This case indeed raises multiple issues that are pertinent to *EGFR*-mutation driven LADC, specifically tumor heterogeneity, development of resistance mechanisms to EGFR TKI, and the importance of repeated genomic testing by tissue or liquid biopsy at every progression. It also highlights the need for effective treatments after progression on osimertinib.

Co-existence of LADC driven by two separate genomic drivers is a rare occurrence and this is highlighted by case report authored by Du *et al.* In this report, the authors

describe the case of a 42-year-old woman who presented with two approximately 2cm synchronous pulmonary lesions in each lung. Initial diagnostics included CT guided biopsy of one lesion and was consistent with LADC with *EGFR* exon 21 L858R point mutation (22). The patient was treated 'neoadjuvantly' with gefitinib for 8 weeks. Evaluation of response by imaging studies showed decrease in size of the biopsied lesion but not the lesion on the contralateral lung. The patient subsequently underwent bilateral surgical resection of both lesions 3 months apart. Post-operative pathological result indicated a diagnosis of two stage I synchronous primary tumors. The second lesion had no *EGFR* mutation but harbored *KIF5B-RET* fusion. While this case points to the success of EGFR TKIs in evoking a response in *EGFR* mutant LADC, it also underscores the importance of genomic testing of individual tumors when the clinical picture is suspicious of two primary lesions. Biopsy of both lesions would have led to diagnosis of synchronous early-stage cancers and curative-intent surgery without any need for systemic treatment. Currently, EGFR TKIs are now incorporated into adjuvant therapy for LADC, but they currently have no established role in the neoadjuvant setting for early-stage LADC (23). The case report, however, underscores the importance of genomic testing of tumors that are clinically or morphologically suspicious for separate primaries.

Surgery is a mainstay modality in the diagnosis and management of lung cancer including *EGFR* mutant cancers. However, as with most invasive procedures, comes with an inherent risk of complications such as infections, air leaks, bleeding, and long term oxygen dependence due to decreased lung capacity. Dai *et al.* describe the case of a noncancer patient whose lobectomy was complicated by infection and a protracted treatment and recovery course, serving as a cautionary tale of the potential morbidity that can be associated with surgery (24). The case brings to attention the need for adequate pre-operative risk assessment, appropriate patient selection and use of minimally invasive surgical approaches whenever possible. It is worth mentioning that emerging technologies such as AI-based radiology reads, complementary biomarker assays may help distinguish between malignant and benign lesions more accurately. Wang *et al.* report one such potentially useful application of a novel localization technology to better visualize and localize a sub centimeter ground glass nodule intraoperatively to enable minimally invasive surgical approach (25). In conclusion, EGFR TKIs have revolutionized the management of LADCs and resulted in improved outcomes in these patients. From the initial years of first-generation EGFR TKIs, great strides have been made in understanding their resistance mechanisms and development of next generation drugs to overcome these, improving their efficacy in combination with other drugs and broadening their applicability now to include use in the adjuvant setting. While it is extremely important to continue exploring novel agents and combinations through clinical trials, these series of case reports reviewed in this manuscript highlight unique clinical scenarios that we frequently face in the real world. Publication of cases such as these and strengthening them by the unique tumor-board like commentary by international experts adds great value to existing literature.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Journal of Thoracic Disease*. The article did not undergo external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-432/coif). CSL reports consulting fees from Pharmacy Times, Annenberg, Health First and Amida Care. CSL reports honoraria for lectures from Pharmacy Times, American College of Clinical Pharmacy, HOPA Annual Conference and HOPA Mentorship Program Update. CSL serves on the advisory board of G1 Therapeutics and Takeda. CSL serves as member of HOPA Publication Committee, President of Long Island Society of Health-System Pharmacists, Chair of NYSCHP Education and Professional Development Committee, and Chair of NYSCHP Oncology Symposium. CSL has no conflicts of interests as it pertains to this manuscript. NS reports honoraria for lectures sponsored by OncLive and Total Health Conferencing. NS serves on the advisory board of AstraZeneca, Blueprint pharma, Takeda, Regeneron, Merck, Genentech, Boehringer Ingram and Mirati. NS serves as a member of Alliance Oncology Preventions Committee, member of Alliance Oncology Respiratory Committee, publications committee of IASLC and virtual mentorship committee of ASCO. NS has no conflicts of interests as it pertains to this manuscript. The

other author has no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Amann J, Kalyankrishna S, Massion PP, et al. Aberrant epidermal growth factor receptor signaling and enhanced sensitivity to EGFR inhibitors in lung cancer. Cancer Res 2005;65:226-35.
2. Rosell R, Moran T, Queralt C, et al. Screening for epidermal growth factor receptor mutations in lung cancer. N Engl J Med 2009;361:958-67.
3. Lee CS, Sharma S, Miao E, et al. A Comprehensive Review of Contemporary Literature for Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors in Non-Small Cell Lung Cancer and Their Toxicity. Lung Cancer (Auckl) 2020;11:73-103.
4. Mok TS, Wu Y-L, Thongprasert S, et al. Gefitinib or Carboplatin– paclitaxel in pulmonary adenocarcinoma. N Engl J Med 2009;361:947-57.
5. Mitsudomi T, Morita S, Yatabe Y, et al. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. Lancet Oncol 2010;11:121-8.
6. Maemondo M, Inoue A, Kobayashi K, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. N Engl J Med 2010;362:2380-88.
7. Zhou C, Wu YL, Chen G, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. Lancet Oncol 2011;12:735-42.
8. U.S. Food and Drug Administration. Center for Drug Evaluation and Research. Resources for Information on Approved Drugs. Accessed April 13, 2022. Available online: https://www.fda.gov/drugs/drug-approvals-and-databases/resources-information-approved-drugs
9. Ramalingam SS, Vansteenkiste J, Planchard D, et al. Overall Survival with Osimertinib in Untreated, EGFR-Mutated Advanced NSCLC. N Engl J Med 2020;382:41-50.
10. Soria JC, Ohe Y, Vansteenkiste J, et al. Osimertinib in Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer. N Engl J Med 2018;378:113-25.
11. Jia Z, Wang Y, Cao L, et al. First-line treatment selection with organoids of an EGFRm + TP53m stage IA1 patient with early metastatic recurrence after radical surgery and follow-up. J Thorac Dis 2020;12:3764-73.
12. Aggarwal C, Davis CW, Mick R, et al. Influence of TP53 Mutation on Survival in Patients With Advanced EGFR-Mutant Non-Small-Cell Lung Cancer. JCO Precis Oncol 2018.
13. Song Y, Jia Z, Wang Y, et al. Potential treatment strategy for the rare osimertinib resistant mutation EGFR L718Q. J Thorac Dis 2020;12:2771-80.
14. Zheng Y, Zhou M, Arulananda S, et al. Management of non-small cell lung cancer with resistance to epidermal growth factor receptor tyrosine kinase inhibitor: case discussion. J Thorac Dis 2020;12:159-64.
15. Zang J, Horinouchi H, Hanaoka J, et al. The role of salvage surgery in the treatment of a gefitinib-resistant non-small cell lung cancer patient: a case report. J Thorac Dis 2021;13:4554-9.
16. Papadimitrakopoulou VA, Mok TS, Han JY, et al. Osimertinib versus platinum-pemetrexed for patients with EGFR T790M advanced NSCLC and progression on a prior EGFR-tyrosine kinase inhibitor: AURA3 overall survival analysis. Ann Oncol 2020;31:1536-44.
17. Mok TS, Wu YL, Ahn MJ, et al. Osimertinib or Platinum-Pemetrexed in EGFR T790M-Positive Lung Cancer. N Engl J Med 2017;376:629-40.
18. Ramalingam SS, Cheng Y, Zhou C, et al. Mechanisms of acquired resistance to first-line osimertinib: preliminary data from the phase III FLAURA study [abstract LBA50]. Ann Oncol 2018;29:viii740.
19. Gray JE, Peled N, Markovets A, et al. Longitudinal circulating tumour DNA (ctDNA) monitoring for early detection of disease progression and resistance in advanced NSCLC in FLAURA [abstract LBA85]. Ann Oncol 2019;30:v921-2.
20. Schoenfeld AJ, Chan JM, Kubota D, et al. Tumor Analyses

Reveal Squamous Transformation and Off-Target Alterations As Early Resistance Mechanisms to First-line Osimertinib in EGFR-Mutant Lung Cancer. Clin Cancer Res 2020;26:2654-63.
21. Passaro A, Jänne PA, Mok T, et al. Overcoming therapy resistance in EGFR-mutant lung cancer. Nat Cancer 2021;2:377-91.
22. Du W, Zhao Y, Xuan Y, et al. Different efficacy in the non-small cell lung cancer patient with bilateral synchronous lesions treated with neoadjuvant gefitinib therapy: a case report. J Thorac Dis 2020;12:1582-7.
23. Wu YL, Tsuboi M, He J, et al. Osimertinib in Resected EGFR-Mutated Non-Small-Cell Lung Cancer. N Engl J Med 2020;383:1711-23.
24. Dai J, Greiffenstein P, Petrella F, et al. Treatment of a lung lobectomy patient with severe post-surgical infection in the anterior thoracic wall by multiple debridement and drainage procedures: a case report. J Thorac Dis 2020;12:7481-7.
25. Wang G, Lin Y, Zheng L, et al. A new method for accurately localizing and resecting pulmonary nodules. J Thorac Dis 2020;12:4973-84.

Cite this article as: Oduah EI, Lee CS, Seetharamu N. The emerging landscape of EFGR tyrosine kinase inhibitors in lung adenocarcinoma—successes and challenges. J Thorac Dis 2022;14(6):1766-1771. doi: 10.21037/jtd-22-432