

# Metastatic lung cancer in the age of targeted therapy: improving long-term survival

Jaydira Del Rivero<sup>1</sup>, Lindsey Enewold<sup>2</sup>, Anish Thomas<sup>3</sup>

<sup>1</sup>Medical Oncology Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA; <sup>2</sup>Healthcare Assessment Research Branch, Healthcare Delivery Research Program, Division of Cancer Control and Population Sciences, National Cancer Institute, Bethesda, MD, USA;

<sup>3</sup>Thoracic and Gastrointestinal Oncology Branch, Center for Cancer Research, National Cancer Institute, Bethesda, MD, USA

*Correspondence to:* Lindsey Enewold, PhD, MPH. NCI Shady Grove, Healthcare Assessment Research Branch, Healthcare Delivery Research Program (HDRP), Division of Cancer Control and Population Sciences (DCCPS), 9609 Medical Center Drive, Room 3E506, Bethesda, MD 20892-9762, USA. Email: [lindsey.ewenold@nih.gov](mailto:lindsey.ewenold@nih.gov).

*Provenance:* This is a Guest Perspective commissioned by Section Editor Guangliang Qiang, MD (Department of Thoracic Surgery, China-Japan Friendship Hospital, Beijing, China).

*Comment on:* Lin JJ, Cardarella S, Lydon CA, *et al.* Five-Year Survival in EGFR-Mutant Metastatic Lung Adenocarcinoma Treated with EGFR-TKIs. *J Thorac Oncol* 2016;11:556-65.

**Abstract:** *Epidermal growth factor receptor (EGFR)* mutations are the most frequent targetable genetic abnormality observed in non-small cell lung cancer (NSCLC). More than a decade after *EGFR* mutations were shown to predict sensitivity to EGFR-tyrosine kinase inhibitors (EGFR-TKI), retrospective cohort studies are now identifying and characterizing 5-year survivors. While these studies indicate subsets of patients achieving long-term survival, there is paucity of data pertaining to the long-term survival benefits of these targeted therapies at a population level. Improving access to molecular testing and treatment are key to maximizing the survival benefits at a population level.

**Keywords:** Lung cancer; epidermal growth factor receptor (EGFR); genetics; erlotinib; survival

Submitted Sep 24, 2016. Accepted for publication Oct 09, 2016.

doi: 10.21037/tlcr.2016.11.08

**View this article at:** <http://dx.doi.org/10.21037/tlcr.2016.11.08>

Lin *et al.* recently estimated and identified factors associated with the 5-year survival rate among patients with *epidermal growth factor receptor (EGFR)*-mutant metastatic lung adenocarcinoma treated with an EGFR-tyrosine kinase inhibitor (TKI) (1). In order to appreciate the relevance of the results, we will briefly review the evolving lung cancer treatment landscape and previous survival estimates. We will then provide our perspective on the necessary next steps to maximize the population-wide survival of this historically recalcitrant cancer.

Lung cancer, the majority of which is non-small cell lung cancer (NSCLC), is the leading cause of cancer death for both men and women in the United States (2). According to the latest data, more than half (55%) of the NSCLC diagnosed in the United States presents at an advanced stage, wherein the 5-year survival rate is only 4.9% (3).

Until the early-2000s, platinum-based chemotherapy was the standard of care for patients with newly diagnosed advanced NSCLC (4). However, responses to chemotherapy were modest at best with randomized clinical trials indicating response rates between 17% and 22% and median overall survival (OS) between 7 and 8 months (4-6). Starting in the mid-2000s, identification of actionable oncogenic driver mutations and mechanisms of resistance to targeted therapeutics have become increasingly important in the management of NSCLC.

The most extensively studied gene in this context is *EGFR*, which has a high prevalence of mutations (10-28%) among NSCLC patients (7). Tumors harboring *EGFR* mutations tend to be highly sensitive to orally active EGFR-TKIs: erlotinib, gefitinib and afatinib (8-12). In patients with advanced disease, randomized clinical trials have

consistently demonstrated improved response rates (56–83%) and progression free survival (9–14 months) with EGFR-TKIs than with standard chemotherapy (9,12,13). The impact of EGFR-TKIs on long-term outcomes has been less consistent. Although several clinical trials have also shown longer OS among patients with *EGFR*-mutant tumors treated with EGFR-TKIs compared to chemotherapy alone, a significant improvement in median OS has only been reported for afatinib (31–33 vs. 18–21 months) (14,15). The lack of an OS advantage has been attributed largely to the crossover design of the clinical trials, indicating that these drugs may be similarly active regardless of line of treatment (12,13,16). Moreover, most of the previous studies have had limited follow-up and/or have not reported long-term survival stratified by EGFR-TKI exposure status. Thus, it has been difficult to determine the true effectiveness of these agents, particularly outside of a clinical trial setting.

With these knowledge gaps in mind, Lin *et al.* sought to estimate and identify factors associated with 5-year survival among patients treated with erlotinib or gefitinib. Briefly, 137 patients from the Dana-Farber Cancer Institute who were diagnosed with *EGFR*-mutant metastatic lung adenocarcinoma between 2002 and 2009, treated with an EGFR-TKI and had completed follow-up for at least 5 years were included in the study. The median OS for these patients was 30.9 months and 20 patients (14.6%) were 5-year survivors. In multivariate analysis, exon 19 deletions, absence of extrathoracic or brain metastasis and non-current smoking status were associated with 5-year survival.

The results from this study are promising and finally indicate that a sizable subset of metastatic NSCLC patients, who can be readily identified, are attaining the previously elusive 5-year survival mark. These results also appear to be in agreement with the reported outcomes from a much larger (n=1,657) multicenter Japanese cohort that included patients with advanced or recurrent *EGFR*-mutant NSCLC who received EGFR-TKI treatment between 2008 and 2012 (17). Briefly, Inoue *et al.* reported a median OS of 30.8 months and an estimated 5-year survival rate of just over 20%. Although there was not complete agreement on which factors were associated with survival, *EGFR* mutation type was again found to be associated with survival.

An important caveat in interpreting the results of these two studies is that the presence of the *EGFR* mutation in itself may be a favorable prognostic marker. Previous studies have shown superior outcomes for patients with *EGFR*-mutant tumors compared to patients without these mutations, irrespective of stage and treatment (18,19).

Thus, restricting studies to *EGFR*-mutant positive patients who are treated with an EGFR-TKI makes it impossible to determine if the survival benefit is due to tumor characteristics and/or treatment.

Although the agreement between these two studies is encouraging, we would advise caution be taken before generalizing the 5-year survival estimates to the population level. In a random sample of over 1,300 NSCLC patients from the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) program, we found that only 16.8% patients overall and 22.6% of stage IV adenocarcinoma patients underwent *EGFR* testing (20). In striking contrast to our series which included patients diagnosed in 2010, the frequency of *EGFR* testing in the Lin *et al.* study was 71%, which again included patients diagnosed between 2002 and 2009. Further, roughly 63% of the patients with *EGFR* mutations received an EGFR-TKI in the Lin *et al.* series compared with only 48% of patients from our series. Although we did not have sufficient follow-up time to estimate 5-year survival, the estimated median OS among the *EGFR*-mutant positive lung adenocarcinoma patients who received an EGFR-TKI in our series was only 23 months. Thereby, although the survival estimates from our population level data also indicate improved outcomes among *EGFR*-mutant positive patients who receive EGFR-TKIs compare to NSCLC patients as a whole, the magnitude of the observed improvement at a population level was attenuated. Variations in observed median OS likely reflect differences in patient demographic, tumor and health characteristics and/or the quality of care received at select institutions compared to the national experience.

Ultimately, access to molecular testing and treatment are key to realizing the benefits of precision oncology—the premise that treatment choices tailored to individual patients using personalized cancer genomic data may markedly improve outcomes—at a population level. Given the profusion of potentially targetable molecular alterations and the complexities of obtaining tissue samples and that of testing, it is important to have a national strategy to facilitate widespread and uniform implementation of molecular profiling. Such nationwide efforts have been reported both from the Europe and the United States. The French Cooperative Thoracic Intergroup study involved over 3,500 clinicians and 28 certified molecular genetics centers covering the whole of France and conducted molecular analyses on tumors from over 17,000 NSCLC patients over a 1-year period (21). In the United States, the Lung Cancer Mutation Consortium analyzed samples using multiplex

genotyping from 700 patients with adenocarcinoma at 14 centers, identifying a targetable driver mutation in over 60% (22). These studies underscore the feasibility of large-scale utilization of molecular profiling in lung cancer.

### Acknowledgements

This work was supported in part by the Intramural Research Program of the National Institutes of Health, National Cancer Institute.

### Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

*Disclaimer:* The content of this article is solely the responsibility of the authors and does not necessarily represent the official views of the National Cancer Institute or the National Institutes of Health.

### References

1. Lin JJ, Cardarella S, Lydon CA, et al. Five-Year Survival in EGFR-Mutant Metastatic Lung Adenocarcinoma Treated with EGFR-TKIs. *J Thorac Oncol* 2016;11:556-65.
2. Siegel R, Ma J, Zou Z, et al. Cancer statistics, 2014. *CA Cancer J Clin* 2014;64:9-29.
3. Howlader N, Noone AM, Krapcho M, et al. editors. SEER Cancer Statistics Review, 1975-2013. National Cancer Institute. Bethesda, MD, based on November 2015 SEER data submission, posted to the SEER web site, April 2016. Available online: [http://seer.cancer.gov/csr/1975\\_2013/sections.html](http://seer.cancer.gov/csr/1975_2013/sections.html)
4. Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N Engl J Med* 2002;346:92-8.
5. Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med* 2006;355:2542-50.
6. Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. *J Clin Oncol* 2008;26:3543-51.
7. Pao W, Miller V, Zakowski M, et al. EGF receptor gene mutations are common in lung cancers from "never smokers" and are associated with sensitivity of tumors to gefitinib and erlotinib. *Proc Natl Acad Sci U S A* 2004;101:13306-11.
8. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med* 2009;361:947-57.
9. 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;362:2380-8.
10. Rosell R, Carcereny E, Gervais R, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol* 2012;13:239-46.
11. 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.
12. 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.
13. Sequist LV, Yang JC, Yamamoto N, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. *J Clin Oncol* 2013;31:3327-34.
14. Yang JC, Sequist LV, Geater SL, et al. Clinical activity of afatinib in patients with advanced non-small-cell lung cancer harbouring uncommon EGFR mutations: a combined post-hoc analysis of LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6. *Lancet Oncol* 2015;16:830-8.
15. Yang JC, Wu YL, Schuler M, et al. Afatinib versus cisplatin-based chemotherapy for EGFR mutation-positive lung adenocarcinoma (LUX-Lung 3 and LUX-Lung 6): analysis of overall survival data from two randomised, phase 3 trials. *Lancet Oncol* 2015;16:141-51.
16. Khozin S, Blumenthal GM, Jiang X, et al. U.S. Food and Drug Administration approval summary: Erlotinib for the first-line treatment of metastatic non-small cell lung cancer with epidermal growth factor receptor exon 19 deletions or exon 21 (L858R) substitution mutations. *Oncologist* 2014;19:774-9.
17. Inoue A, Yoshida K, Morita S, et al. Characteristics and overall survival of EGFR mutation-positive non-small cell lung cancer treated with EGFR tyrosine kinase inhibitors:

- a retrospective analysis for 1660 Japanese patients. *Jpn J Clin Oncol* 2016;46:462-7.
18. Eberhard DA, Johnson BE, Amler LC, et al. Mutations in the epidermal growth factor receptor and in KRAS are predictive and prognostic indicators in patients with non-small-cell lung cancer treated with chemotherapy alone and in combination with erlotinib. *J Clin Oncol* 2005;23:5900-9.
  19. Sasaki H, Shimizu S, Endo K, et al. EGFR and erbB2 mutation status in Japanese lung cancer patients. *Int J Cancer* 2006;118:180-4.
  20. Enewold L, Thomas A. Real-World Patterns of EGFR Testing and Treatment with Erlotinib for Non-Small Cell Lung Cancer in the United States. *PLoS One* 2016;11:e0156728.
  21. Barlesi F, Mazieres J, Merlio JP, et al. Routine molecular profiling of patients with advanced non-small-cell lung cancer: results of a 1-year nationwide programme of the French Cooperative Thoracic Intergroup (IFCT). *Lancet* 2016;387:1415-26.
  22. Kris MG, Johnson BE, Berry LD, et al. Using multiplexed assays of oncogenic drivers in lung cancers to select targeted drugs. *JAMA* 2014;311:1998-2006.

**Cite this article as:** Del Rivero J, Enewold L, Thomas A. Metastatic lung cancer in the age of targeted therapy: improving long-term survival. *Transl Lung Cancer Res* 2016;5(6):727-730. doi: 10.21037/tlcr.2016.11.08