

Treating acquired resistance to EGFR-tyrosine kinase inhibitors: still a work in progress

Nathan A. Pennell

Assistant Professor, Solid Tumor Oncology, Cleveland Clinic Taussig Cancer Institute, 9500 Euclid Ave., R-35, Cleveland, OH 44195, USA

Corresponding to: Nathan A. Pennell, MD, PhD. Assistant Professor, Solid Tumor Oncology, Cleveland Clinic Taussig Cancer Institute, 9500 Euclid Ave., R-35, Cleveland, OH 44195, USA. Tel: +216-445-9282; Fax: +216-444-9464. Email: penneln@ccf.org.

Abstract: While most patients with metastatic non-small cell lung cancer (NSCLC) containing sensitizing mutations in the epidermal growth factor receptor (EGFR) gene will achieve an objective response to EGFR tyrosine kinase inhibitors (TKIs) such as erlotinib or gefitinib, patients inevitably develop resistance to these agents. One of the strategies being tested to overcome acquired resistance to EGFR TKIs is the use of irreversible EGFR inhibitors such as afatinib. In the randomized phase 2b/3 LUX-Lung 1 trial in advanced NSCLC patients who progressed after at least 12 weeks of benefit from EGFR TKIs, afatinib failed to improve overall survival compared to placebo. Although the liberal entry criteria likely allowed the inclusion of some patients without true acquired resistance, the failure of this study calls into question the viability of irreversible EGFR inhibitors in this patient population.

Key Words: EGFR; acquired resistance; tyrosine kinase inhibitors



Submitted Apr 25, 2012. Accepted for publication May 28, 2012.

DOI: 10.3978/j.issn.2218-6751.2012.05.01

Scan to your mobile device or view this article at: <http://www.tlcr.org/article/view/408/797>

The last decade has seen major progress in the understanding of non-small cell lung cancer (NSCLC), with the growing recognition that NSCLC is not a single disease but rather a collection of many different subgroups with identifiable and potentially targetable genetic lesions. The first targetable driver mutations were sensitizing mutations in the tyrosine kinase domain of the epidermal growth factor receptor (*EGFR*) gene (1,2), now known to be present in about 10% of NSCLC in Caucasian patients and conferring a high degree of responsiveness to the oral tyrosine kinase inhibitors (TKIs) erlotinib and gefitinib (3). A number of prospective clinical trials have now established that EGFR TKIs induce objective responses in about 70% of patients whose tumors harbor mutations, with a significantly increased median progression free survival (PFS) compared to cytotoxic chemotherapy (4). Nonetheless, most of these patients will eventually progress despite TKI therapy, a phenomenon termed acquired resistance (AR).

Acquired resistance to EGFR TKIs can be achieved through a number of different mechanisms. The most

common mechanism (50%) is the development of a secondary T790M mutation in exon 20 of the *EGFR* gene (5). Other less common mechanisms include increased signaling through parallel receptor tyrosine kinases such as the MET (6) and transformation into a small cell phenotype (7). Presumably this heterogeneity of mechanisms would make a single approach unlikely to be successful at overcoming AR, but nonetheless a number of strategies have been proposed and are being tested in randomized trials. One such strategy is the use of second-generation EGFR inhibitors such as XL 647 (Exelixis Inc., San Francisco, CA) and irreversible pan-HER inhibitors such as neratinib (HKI-272; Wyeth/Pfizer, New London, CT), PF00299804 (Pfizer), and afatinib (BIBW 2,992; Boehringer Ingelheim Pharma GmbH, Ingelheim, Germany). Although these agents have shown some ability to inhibit T790M mutant NSCLC in vitro (8,9), evidence of clinical activity of these agents in patients with AR is lacking (10,11).

The LUX-Lung 1 trial was a randomized, double-blind, international phase 2b/3 trial of single agent afatinib versus

placebo in 585 patients with advanced lung adenocarcinoma who had not progressed after at least 12 weeks of treatment with either erlotinib or gefitinib. This study population was intended to represent a clinically defined group with AR to EGFR TKIs, and the primary endpoint was overall survival. Although the response rate (7% versus 0.5%) and PFS (3.3 *vs.* 1.1 months; $P < 0.0001$) were improved in the afatinib group compared to placebo, there was no difference in median overall survival (OS) between the arms (10.8 months for afatinib *vs.* 12 months for placebo; $P = 0.74$) (12). Of note, tissue was not required for entry in the study, and as a result only 141 of the 585 pts (24%) had tissue available for analysis. Of those, 68% were found to have EGFR mutations, evenly split between the treatment and control arms. Only 8 patients (4 in the afatinib arm) had identifiable T790M mutations, and no other known mechanisms of AR were tested.

The intent of the study investigators was to test the efficacy of afatinib in patients with EGFR mutant lung cancer who had developed AR, but the way they went about it was problematic. For one thing, they did not require testing for *EGFR* mutations prior to enrollment, which diluted the study sample with patients with wild-type *EGFR* who would perhaps be less likely to benefit from an irreversible EGFR TKI. Second, efforts have been made to rigorously define clinical acquired resistance to EGFR TKIs, to allow maximum enrichment of patients in trials such as the LUX-Lung study. The most widely accepted definition is the Jackman definition: prior treatment with a single-agent EGFR TKI and either or both of the following: a tumor that harbors an *EGFR* mutation or objective clinical benefit from treatment with an EGFR TKI (PR/CR or stable disease for ≥ 6 months); systemic progression of disease while on continuous treatment with the TKI within the last 30 days; and no intervening systemic therapy between cessation of the TKI and initiation of new therapy (13). By this strict definition only 34% of patients in the afatinib arm (*vs.* 42% in the placebo arm) would have had true AR, and the magnitude of benefit was indeed numerically higher in this group with a PFS of 4.5 *vs.* 1 month although not statistically significant.

So are we able to draw any conclusions at all from this trial? The liberal definition of AR, the lack of tissue testing to determine mutational status and mechanisms of resistance, and the high degree of subsequent treatment (68% and 79% in the afatinib and placebo arms) combined to muddy the waters. However, if we extrapolate from

the minority of patients with available tissue, then we can assume that most patients had tumors with *EGFR* mutations and that most had AR of one mechanism or another. If that is the case then this study, along with the prior failure of neratinib to show benefit in this population (11), casts doubt on the strategy of using irreversible EGFR TKIs as monotherapy in patients with AR.

Interestingly, there is preliminary evidence that afatinib has activity in AR, including T790M, when combined with the anti-EGFR antibody cetuximab (Imclone, owned by Eli Lilly and Company, New York, NY and Bristol-Myers Squibb Company, Princeton, NJ) (14). We know that cetuximab combined with erlotinib has no activity in the AR population (15), raising the intriguing idea that irreversible EGFR inhibitors may have promise in AR when combined with other agents. More mature, peer reviewed results from this trial are anxiously awaited. The indisputable lessons from LUX-Lung 1, however, are that future trials in the EGFR TKI acquired resistance population must be rigorous in defining their target population, and that every patient enrolled must have tissue available for molecular testing so that clear conclusions can be made from the results.

Acknowledgements

Disclosure: This manuscript is my original work and not submitted for publication elsewhere. I have served as a consultant for Oncogenex and for Teva Pharmaceuticals in the past year. I have served as a consultant for Boehringer Ingelheim which is relevant to this manuscript, but not in the past 2 years.

References

1. Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med* 2004;350:2129-39.
2. Paez JG, Jänne PA, Lee JC, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science* 2004;304:1497-500.
3. Sequist LV, Bell DW, Lynch TJ, et al. Molecular Predictors of Response to Epidermal Growth Factor Receptor Antagonists in Non-Small-Cell Lung Cancer. *J Clin Oncol* 2007;25:587-95.
4. Bria E, Milella M, Cuppone F, et al. Outcome of advanced NSCLC patients harboring sensitizing EGFR mutations randomized to EGFR tyrosine kinase inhibitors or

- chemotherapy as first-line treatment: a meta-analysis. *Ann Oncol* 2011;22:2277-85.
5. Kobayashi S, Boggon TJ, Dayaram T, et al. EGFR mutation and resistance of non-small-cell lung cancer to gefitinib. *N Engl J Med* 2005;352:786-92.
 6. Engelman JA, Zejnullahu K, Mitsudomi T, et al. MET amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling. *Science* 2007;316:1039-43.
 7. Sequist LV, Waltman BA, Dias-Santagata D, et al. Genotypic and Histological Evolution of Lung Cancers Acquiring Resistance to EGFR Inhibitors. *Science Translational Medicine* 2011;3:75ra26.
 8. Gendreau SB, Ventura R, Keast P, et al. Inhibition of the T790M gatekeeper mutant of the epidermal growth factor receptor by EXEL-7647. *Clin Cancer Res* 2007;13:3713-23.
 9. Li D, Ambrogio L, Shimamura T, et al. BIBW2992, an irreversible EGFR/HER2 inhibitor highly effective in preclinical lung cancer models. *Oncogene* 2008;27:4702-11.
 10. Pietanza MC, Lynch TJ Jr, Lara PN Jr, et al. XL647--a multitargeted tyrosine kinase inhibitor: results of a phase II study in subjects with non-small cell lung cancer who have progressed after responding to treatment with either gefitinib or erlotinib. *J Thorac Oncol* 2012;7:219-26.
 11. Sequist LV, Besse B, Lynch TJ, et al. Neratinib, an irreversible pan-ErbB receptor tyrosine kinase inhibitor: results of a phase II trial in patients with advanced non-small-cell lung cancer. *J Clin Oncol* 2010;28:3076-83.
 12. Miller VA, Hirsh V, Cadranel J, et al. Afatinib versus placebo for patients with advanced, metastatic non-small-cell lung cancer after failure of erlotinib, gefitinib, or both, and one or two lines of chemotherapy (LUX-Lung 1): a phase 2b/3 randomised trial. *Lancet Oncol* 2012;13:528-38.
 13. Jackman D, Pao W, Riely GJ, et al. Clinical Definition of Acquired Resistance to Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors in Non-Small-Cell Lung Cancer. *J Clin Oncol* 2010;28:357-60.
 14. Janjigian YY, Groen HJ, Horn L, et al. Activity and tolerability of afatinib (BIBW 2992) and cetuximab in NSCLC patients with acquired resistance to erlotinib or gefitinib. *J Clin Oncol* 2011;29:abstr 7525.
 15. Janjigian YY, Azzoli CG, Krug LM, et al. Phase I/II trial of cetuximab and erlotinib in patients with lung adenocarcinoma and acquired resistance to erlotinib. *Clin Cancer Res* 2011;17:2521-7.

Cite this article as: Pennell NA. Treating acquired resistance to EGFR-tyrosine kinase inhibitors: still a work in progress. *Transl Lung Cancer Res* 2012;1(2):149-151. DOI: 10.3978/j.issn.2218-6751.2012.05.01