Editorial

Epidermal growth factor receptor tyrosine kinase inhibitors in non-small cell lung cancer: a decade of progress and hopeful future

Kumar Rajagopalan[1], Ramaswamy Govindan[2,3]

[1]Department of Medicine, Cooper Medical School of Rowan University, Camden, NJ 08103, USA; [2]Division of Oncology, Washington University School of Medicine, St. Louis, MO 63021, USA; [3]Alvin J. Siteman Cancer Center, St. Louis, MO, USA

Correspondence to: Ramaswamy Govindan, MD. Division of Oncology, Washington University School of Medicine, 660 S. Euclid, Box 8056, St. Louis, MO 63021, USA. Email: rgovinda@dom.wustl.edu.

Submitted Jan 07, 2015. Accepted for publication Jan 12, 2015.
doi: 10.3978/j.issn.2072-1439.2015.01.53
View this article at: http://dx.doi.org/10.3978/j.issn.2072-1439.2015.01.53

Nearly 50% of patients with non-small cell lung cancer (NSCLC) are found to have metastatic disease at presentation (1). Platinum doublet chemotherapy remains the standard initial treatment for the vast majority of patients with advanced NSCLC who have a good performance status. Approximately 10% of patients with advanced NSCLC have activating mutations in the epidermal growth factor receptor tyrosine kinase (*EGFR* TK) in the tumor tissues (2). Significant progress has been made with molecularly targeted therapies in lung cancer since the initial discovery linking the presence of certain *EGFR* TK mutations with exquisite responsiveness to *EGFR* tyrosine kinase inhibitor (TKI) gefitinib (3,4). Although erlotinib, another *EGFR* TKI, has been approved for use in patients with advanced NSCLC who have progressive disease after platinum doublet therapy based on the randomized study sponsored by the National Cancer Institute (NCI)-Canada, it is evident now that the impressive clinical benefit from EGFR TKIs is seen almost exclusively in patients whose tumor cells demonstrate specific mutations in the *EGFR* TK domain (5).

The IPASS trial first established the superiority of gefitinib in significantly prolonging progression free survival (PFS) over standard chemotherapy when used as a first line therapy in patients with *EGFR* mutant lung adenocarcinoma (6). The phase III EURTAC trial conducted in Europe was the first trial to demonstrate the superiority of erlotinib over chemotherapy in previously untreated patients with advanced NSCLC with either the exon 19 deletion or exon 21 L858R mutation (7). The median PFS was 9.7 months for erlotinib versus 5.2 months for platinum based chemotherapy. Two studies have reported improvements in median PFS with an irreversible *EGFR* TK inhibitor, afatinib compared to chemotherapy in patients with *EGFR* mutant lung adenocarcinoma (8,9). Furthermore, initial therapy with afatinib improved overall survival (OS) compared to platinum based doublets in the subset of patients with exon 19 deletion in both these studies.

On the other hand *EGFR* TK inhibitors have consistently been found not to be superior to chemotherapy in patients with advanced NSCLC with *EGFR* wild type or when the *EGFR* mutation status is unknown. INTEREST trial showed gefitinib to be non-inferior to docetaxel (HR: 1.020, 96% CI, 0.905-1.150) with a median OS (7.6 *vs.* 8.0 months, respectively) (10,11). The DELTA study published recently once again confirms the lack of superiority of erlotinib over docetaxel in patients without known *EGF*R activating mutations (12). Of 301 patients enrolled from Japan, 151 were assigned to erlotinib 150 mg/day or docetaxel 60 mg/m^2 every 3 weeks. Patients with advanced NSCLC who had received one or two prior chemotherapy regimens were enrolled in this study. Majority of patients enrolled in this study had EGFR wild type. Not surprisingly, the median PFS for erlotinib was 2.0 months compared to 3.2 months for docetaxel [hazard ratio (HR) 1.22; 95% CI, 0.97-1.55; P=0.09]. The median OS was 14.8 months for erlotinib and 12.2 months for docetaxel (HR, 0.91; 95% CI, 0.68-1.22; P=0.53). Other investigators have reported similar findings (13-15). As we move forward, significant progress in the treatment of lung cancer can only be made with a better understanding of the molecular alterations underlying tumor evolution particularly in response to targeted therapies, improved drug development process and effective use of

immunotherapy. Finally we should evaluate the potential benefits of using molecularly targeted agents in early stage and locally advanced NSCLC in order to improve the cure rates.

Advances in genomic sequencing have now made it possible to discover molecular alterations present in malignant cells in great detail and precision (16-18). It is now clear that lung cancer associated with tobacco smoking results in complex genomic alterations including a number of single nucleotide variations, insertions, deletions, copy number alterations and structural rearrangements. Several institutional studies and The Cancer Genome Atlas (TCGA) project have reported novel potentially actionable alterations in lung adenocarcinoma.

On a very encouraging note, several large-scale innovative studies are currently ongoing to define the role of targeted agents in molecularly selected groups of patients with early and locally advanced NSCLC. The adjuvant lung cancer enrichment marker identification and sequencing trials (ALCHEMIST) will screen nearly 8,000 patients with completely resected lung adenocarcinoma for *EGFR* mutations and EML4-*ALK* rearrangement in a central laboratory (NCT02194738). Patients with *EGFR* mutations or *ALK* rearrangement will be randomized to specific molecularly targeted therapy (erlotinib or crizotinib) or placebo following standard post-operative therapy (NCT02193282; NCT02201992). The primary endpoint of the study is OS. Comprehensive genomic analyses will be performed on tumor specimens from patients enrolled in this trial. The role of molecularly targeted agents in patients with unresectable locally advanced NSCLC is being studied in an ongoing multi-center study (NCT01822496). In this study, patients with *EGFR* mutant lung adenocarcinoma will receive either induction therapy for three months with erlotinib followed by definitive chemoradiation or chemoradiation alone. Similarly patients with *ALK* positive locally advanced NSCLC will receive either induction therapy with crizotinib followed by chemoradiation or chemoradiation alone.

It is likely that a number of novel treatment options will soon be available for patients with *EGFR* mutant and *ALK* positive NSCLC. Promising results have been reported now in patients with acquired resistance to EGFR inhibitors and ALK inhibitors (19,20). AZD 9291, a third generation EGFR TKI produced an impressive response rate of 64% among 107 patients with centrally confirmed *EGFR* T790M. A similar study using a different compound, CO-1686 reported a response rate of 58% in 40 patients with centrally confirmed *EGFR* T790M. The median PFS had not been reached at the time of presentation and was estimated to exceed one year. Several ongoing clinical trials are now available for patients with *EGFR* mutant NSCLC prior to and after therapy with first generation EGFR TKIs.

Finally, genomic analyses of multiple regions from the primary tumor reveal significant intra-tumoral heterogeneity in lung cancer (21-23). Tumor clones evolve either in a linear fashion by acquiring progressively fitter clones, or follow a branched pattern where multiple sub clones thrive simultaneously, resulting in a complex heterogeneous tumor. A better understanding of clonal evolution in response to therapy is critical to optimally treat acquired resistance. Studies with AZD 9291 and CO 1086 underscore the importance of genotyping growing lesions following targeted therapy in the salvage setting. Hopefully genotyping of cell free DNA from plasma would make the process of serial molecular evaluation easier in the coming years. While much work remains to be done, it is heartening to see the pace of progress in cancer therapy that we have witnessed over the past few years.

Acknowledgements

Disclosure: R Govindan has been a consultant for Genentech, Boehringer Ingelheim, Clovis Oncology.

References

1. Siegel R, Ma J, Zou Z, et al. Cancer statistics, 2014. CA Cancer J Clin 2014;64:9-29.
2. Oxnard GR, Binder A, Jänne PA. New targetable oncogenes in non-small-cell lung cancer. J Clin Oncol 2013;31:1097-104.
3. 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.
4. 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.
5. Tsao MS, Sakurada A, Cutz JC, et al. Erlotinib in lung cancer - molecular and clinical predictors of outcome. N Engl J Med 2005;353:133-44.
6. Fukuoka M, Wu YL, Thongprasert S, et al. Biomarker analyses and final overall survival results from a phase III, randomized, open-label, first-line study of gefitinib versus carboplatin/paclitaxel in clinically selected patients with advanced non-small-cell lung cancer in Asia (IPASS). J

Clin Oncol 2011;29:2866-74.
7. 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.
8. 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.
9. Wu YL, Zhou C, Hu CP, et al. Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-Lung 6): an open-label, randomised phase 3 trial. Lancet Oncol 2014;15:213-22.
10. Douillard JY, Shepherd FA, Hirsh V, et al. Molecular predictors of outcome with gefitinib and docetaxel in previously treated non-small-cell lung cancer: data from the randomized phase III INTEREST trial. J Clin Oncol 2010;28:744-52.
11. Kim ES, Hirsh V, Mok T, et al. Gefitinib versus docetaxel in previously treated non-small-cell lung cancer (INTEREST): a randomised phase III trial. Lancet 2008;372:1809-18.
12. Kawaguchi T, Ando M, Asami K, et al. Randomized phase III trial of erlotinib versus docetaxel as second- or third-line therapy in patients with advanced non-small-cell lung cancer: Docetaxel and Erlotinib Lung Cancer Trial (DELTA). J Clin Oncol 2014;32:1902-8.
13. Maruyama R, Nishiwaki Y, Tamura T, et al. Phase III study, V-15-32, of gefitinib versus docetaxel in previously treated Japanese patients with non-small-cell lung cancer. J Clin Oncol 2008;26:4244-52.
14. Karampeazis A, Voutsina A, Souglakos J, et al. Pemetrexed versus erlotinib in pretreated patients with advanced non-small cell lung cancer: a Hellenic Oncology Research Group (HORG) randomized phase 3 study. Cancer 2013;119:2754-64.
15. Ciuleanu T, Stelmakh L, Cicenas S, et al. Efficacy and safety of erlotinib versus chemotherapy in second-line treatment of patients with advanced, non-small-cell lung cancer with poor prognosis (TITAN): a randomised multicentre, open-label, phase 3 study. Lancet Oncol 2012;13:300-8.
16. Govindan R, Ding L, Griffith M, et al. Genomic landscape of non-small cell lung cancer in smokers and never-smokers. Cell 2012;150:1121-34.
17. Cancer Genome Atlas Research Network. Comprehensive molecular profiling of lung adenocarcinoma. Nature 2014;511:543-50.
18. Imielinski M, Berger AH, Hammerman PS, et al. Mapping the hallmarks of lung adenocarcinoma with massively parallel sequencing. Cell 2012;150:1107-20.
19. Janne PA, Ramalingam SS, Yang J, et al. Clinical activity of the mutant-selective EGFR inhibitor AZD9291 in patients (pts) with EGFR inhibitor–resistant non-small cell lung cancer (NSCLC). J Clin Oncol 2014;32:abstr 8009.
20. Sequist LV, Soria JC, Gadgeel SM, et al. First-in-human evaluation of CO-1686, an irreversible, highly selective tyrosine kinase inhibitor of mutations of EGFR (activating and T790M). J Clin Oncol 2014;32:abstr 8010.
21. de Bruin EC, McGranahan N, Mitter R, et al. Spatial and temporal diversity in genomic instability processes defines lung cancer evolution. Science 2014;346:251-6.
22. Govindan R. Cancer. Attack of the clones.Science 2014;346:169-70.
23. Zhang J, Fujimoto J, Zhang J, et al. Intratumor heterogeneity in localized lung adenocarcinomas delineated by multiregion sequencing. Science 2014;346:256-9.

Cite this article as: Rajagopalan K, Govindan R. Epidermal growth factor receptor tyrosine kinase inhibitors in non-small cell lung cancer: a decade of progress and hopeful future. J Thorac Dis 2015;7(3):217-219. doi: 10.3978/j.issn.2072-1439.2015.01.53

