Editorial

Epidermal growth factor tyrosine kinase inhibitor therapy inferior to second-line chemotherapy in EGFR wild-type non-small cell lung cancer patients: results of French nationwide observational study

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In the recent issue of *The European Respiratory Journal*, Tomasini *et al.* report on an observational study comparing the clinical, biological, treatment and outcome data for epidermal growth factor wild-type (EGFR-wt) advanced non-small cell lung cancer (NSCLC) patients who received second-line treatment with an EGFR tyrosine kinase inhibitor (TKI) versus those that received second-line chemotherapy, collected in France over a 1 year period (1). Their central finding, that clinical outcomes with second-line EGFR TKI therapy in EGFR-wt patients were inferior to those with second-line chemotherapy, underscores the ineffectual nature of the treatment of EGFR-wt NSCLC with an EGFR TKI.

Data for Tomasini *et al.*'s study were generated from the French Cooperative Thoracic Intergroup (IFCT), representing a nationwide approach to genetic tumor profiling of NSCLC at 28 molecular genetics centers throughout France from April 2012–April 2013. The 868 EGFR-wt patients treated with second-line chemotherapy had a median PFS of 4.3 *vs.* 2.83 months in the 410 patients treated with second-line TKI (HR 0.66; 95% CI: 0.57–0.77; P<0.0001) and median OS was longer in the chemotherapy group at 8.38 *vs.* 4.99 months in the EGFR TKI group (HR 0.70; 95% CI: 0.59–0.83; P<0.0001). A clear limitation of this study, which the authors acknowledge, is its observational nature leading to demographic imbalances between the two treatment arms (1).

Specifically, more non-smoking, ECOG performance status ≥2, elderly (≥65 years old) patients were treated with an EGFR TKI, rather than chemotherapy (nonsmokers: 16.3% in TKI group *vs.* 8.8% in chemotherapy group, P<0.0001; ECOG ≥2: 27.1% in TKI group *vs.* 18.2% in chemotherapy group, P<0.0001; age ≥65 years old: 46.8% in TKI group *vs.* 32.7% in chemotherapy group, P<0.0001). This is not surprising, since EGFR TKIs are generally considered to be less toxic than cytotoxic chemotherapy and were thus likely preferentially selected by clinicians in frail patients and non-smokers. However, when controlling for these confounding characteristics, the survival benefit observed in the chemotherapy group remained (1).

Although the efficacy of an EGFR TKI in NSCLC was first established in a biomarker agnostic fashion (2), subsequent studies have prospectively evaluated the relevance of an EGFR mutation in relation to EGFR TKI response. The landmark IPASS (Iressa Pan-Asia Study) compared gefitinib with carboplatin/paclitaxel as first-line therapy in advanced NSCLC. The findings of the study were striking, with EGFR-mutant (EGFR-mt) patients evidencing a 71.2% objective response rate (ORR) compared to 1.1% in EGFR-wt patients (P=0.001) (3).

In the TAILOR (Tarceva Italian Lung Optimization Trail), erlotinib was compared to docetaxel in EGFR-wt patients as second line therapy and the ORR in EGFR-wt patients to erlotinib was only 3.0%, compared to 15.5% in the docetaxel arm (P=0.003) (4). This difference in ORR between the two treatment arms translated into a median OS of 8.2 months in the docetaxel arm compared to 5.4 months in the erlotinib arm (adjusted HR 0.73; 95% CI: 0.53–1.00; P=0.05), similar to the OS benefit observed in the current study (4). In the U.S., EGFR TKIs are no longer approved for use in EGFR-wt patients (5). In October 2016, the U.S. FDA modified erlotinib's indication, limiting its use to only those patients whose tumors harbor an EGFR mutation, based upon the IUNO trial that found that overall survival with maintenance erlotinib was no better than placebo as second-line therapy in EGFR-wt patients (5,6).

Tomasini *et al.*'s observational study presented in the recent issue of *The European Respiratory Journal* further emphasizes the inferior nature of TKI therapy in EGFR-wt patients. Importantly, a number of more appealing therapeutic options are currently available as second-line therapies in EGFR-wt patients, including immunotherapy, chemotherapy +/– angiogenesis inhibitors, and single agent chemotherapy (7-10). In the current treatment landscape there appears to be no role for an EGFR TKI in the treatment of EGFR-wt patients.

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Footnote

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

References

1. Tomasini P, Brosseau S, Mazières J, et al. EGFR tyrosine kinase inhibitors versus chemotherapy in EGFR wild-type pre-treated advanced nonsmall cell lung cancer in daily practice. Eur Respir J 2017;50. pii: 1700514.
2. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med 2005;353:123-32.
3. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 2009;361:947-57.
4. Garassino MC, Martelli O, Broggini M, et al. Erlotinib versus docetaxel as second-line treatment of patients with advanced non-small-cell lung cancer and wild-type EGFR tumours (TAILOR): a randomised controlled trial. Lancet Oncol 2013;14:981-8.
5. Approved Drugs - Erlotinib (Tarceva). In: U S Food and Drug Administration Home Page. US FDA. Available online: www.fda.gov/drugs/informationondrugs/approveddrugs/ucm525739.htm
6. Cicènas S, Geater SL, Petrov P, et al. Maintenance erlotinib versus erlotinib at disease progression in patients with advanced non-small-cell lung cancer who have not progressed following platinum-based chemotherapy (IUNO study). Lung Cancer 2016;102:30-7.
7. Garon EB, Rizvi NA, Hui R, et al. Pembrolizumab for the Treatment of Non–Small-Cell Lung Cancer. N Engl J Med 2015;372:2018-28.
8. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non–Small-Cell Lung Cancer. N Engl J Med 2015;373:1627-39.
9. Garon EB, Ciuleanu TE, Arrieta O, et al. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. Lancet 2014;384:665-73.
10. Shepherd FA, Dancey J, Ramlau R, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. J Clin Oncol 2000;18:2095-103.

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