Editorial Commentary

Implications of the success of EGFR-targeted therapy in advanced non–small cell lung cancer for its application to the adjuvant setting

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

Comment on: Liang W, Cai K, Chen C, *et al.* Society for Translational Medicine consensus on postoperative management of EGFR-mutant lung cancer (2019 edition). Transl Lung Cancer Res 2019;8:1163-73.

Submitted Apr 01, 2020. Accepted for publication Apr 14, 2020.
doi: 10.21037/jtd-2020-46
View this article at: http://dx.doi.org/10.21037/jtd-2020-46

Epidermal growth factor receptor gene (*EGFR*) kinase domain mutations are a driving force for a substantial proportion of non-small cell lung cancer (NSCLC) tumors. The prevalence of such mutations in individuals with such tumors differs among ethnic groups and geographic regions, ranging from ~10 to 15% in Caucasians up to ~40% to 60% in Asians. Monotherapy with 1st-generation (gefitinib, erlotinib) or 2nd-generation (afatinib) EGFR tyrosine kinase inhibitors (TKIs) had become the standard treatment option for patients with advanced or metastatic NSCLC harboring such mutations, with several randomized phase III studies having shown that front-line EGFR-TKIs confers an improved progression-free survival compared with platinum-based cytotoxic chemotherapy in this setting (1-4). However, the third-generation drug osimertinib has now been established as the preferred EGFR-TKI for chemotherapy-naïve *EGFR*-mutated NSCLC, given that the FLAURA study demonstrated its superiority over the first-generation agents gefitinib and erlotinib (5). The success of EGFR-targeted therapy for *EGFR*-mutated advanced NSCLC has allowed researchers to turn their attention to the potential of this approach for the adjuvant setting. Platinum-based doublet therapy has been the standard of care for patients with NSCLC of stage II or IIIA who undergo complete tumor resection regardless of *EGFR* mutation status. However, individuals who receive such adjuvant chemotherapy have shown an improvement of only 4 to 5 percentage points in 5-year overall survival rate compared with those receiving surgery alone (6).

Liang *et al.* have recently summarized the indications for EGFR-TKI therapy in patients with completely resected *EGFR*-mutated NSCLC (7). This expert consensus aimed to review the recent evidence and to offer recommendations on key issues relating to such treatment. The consensus was based largely on the results of several randomized phase II or III studies including the RADIANT, ADJUVANT, and EVAN studies. The RADIANT study investigated adjuvant erlotinib therapy administered for 2 years in patients with resected stage IB to IIIA NSCLC whose tumors were found to overexpress EGFR protein measured by IHC or to manifest *EGFR* gene amplification by FISH. It found that adjuvant erlotinib did not significantly improve disease-free survival (DFS) versus placebo in these biomarker-selected patients (8). Although subset analysis showed a trend toward a better DFS in favor of erlotinib in patients with activating mutations of *EGFR*, the difference was not statistically significant. In the ADJUVANT study, completely resected stage II to IIIA NSCLC patients positive for *EGFR* mutations were randomized to receive either gefitinib monotherapy for 2 years or cisplatin plus vinorelbine for four cycles. Median DFS was significantly longer for patients treated with gefitinib than for those treated with vinorelbine plus cisplatin (9). The EVAN study evaluated erlotinib therapy for 2 years compared with

four cycles of vinorelbine plus cisplatin in patients with resected *EGFR*-mutated NSCLC of stage IIIA, finding that adjuvant erlotinib improved the 2-year DFS rate and had a better tolerability profile compared with the cytotoxic chemotherapy (10). In Japan, the WJOG6410L study, with a design similar to that of the ADJUVANT trial, is ongoing for evaluation of gefitinib monotherapy versus cisplatin in combination vinorelbine with in patients with surgically resected *EGFR* mutation–positive NSCLC of stage II or III.

On the basis of the results of these various randomized trials, EGFR-TKIs are now a adjuvant treatment option for patients with stage II to IIIA *EGFR*-mutated NSCLC, particularly for those at high risk for recurrence or will be associated with poor tolerance of chemotherapy, with an evidence level of 1 and strong recommendation. However, the Kaplan-Meier curves for DFS in the ADJUVANT study separated at ~12 months and then converged at ~36 months, with no apparent tail of nonprogressors in the gefitinib group, suggesting that adjuvant EGFR-TKI therapy in resected *EGFR* mutation–positive NSCLC patients might not have curative power, even though long-term remission was noted during such treatment.

Regarding the ideal duration of EGFR-TKI treatment in the adjuvant setting, the expert panel proposed that the postoperative therapy should last at least 2 years, with an evidence level of 2B and strong recommendation, given the results of the ADJUVANT study for evaluation of 2-year adjuvant treatment with gefitinib. However, the DFS curve for the gefitinib-treated patients showed a significant downward trend after 2 years, which would be associated with their discontinuation. The appropriate dosing duration therefore needs to be evaluated by further studies.

In summary, the effectiveness of EGFR-targeted therapy for advanced NSCLC has supported investigation of the potential of this approach for the perioperative setting. Several randomized trials have been published or are ongoing for evaluation of EGFR-TKI adjuvant therapy in patients with surgically resected *EGFR*-mutated NSCLC. The results to date, however, suggest that this approach may not increase the cure rate.

Acknowledgments

Funding: None.

Footnote

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jtd-2020-46). MT reports other from Boehringer Ingelheim, other from Chugai Pharmaceutical, other from AstraZeneca, other from Ono Pharmaceutical, other from Novartis, during the conduct of the study.

Ethical statement: The author is 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.

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Cite this article as: Takeda M. Implications of the success of EGFR-targeted therapy in advanced non–small cell lung cancer for its application to the adjuvant setting. J Thorac Dis 2020;12(8):4553-4555. doi: 10.21037/jtd-2020-46