Potential of combination therapy in EGFR mutated lung cancer

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Provenance and Peer Review: This article is commissioned and reviewed by the Section Editor Dr. Song Xu (Department of lung cancer surgery, Tianjin Medical University General Hospital; Tianjin Key Laboratory of Lung Cancer Metastasis and Tumor Microenvironment, Lung Cancer Institute, Tianjin, China).

Response to: Horinouchi H. To combine or not to combine: anti-vascular endothelial growth factor therapies in EGFR mutation positive non-small cell lung cancer. Ann Transl Med 2020. [Epub ahead of print]. doi: 10.21037/atm.2020.01.66

Adderley H, Ackermann CJ, Califano R. Erlotinib plus bevacizumab for EGFR-mutant advanced nonsquamous non-small-cell lung cancer patients: ready for firstline? Ann Transl Med 2019;7:S346.

Submitted Feb 22, 2020. Accepted for publication Mar 28, 2020.

doi: 10.21037/atm.2020.03.76

View this article at: http://dx.doi.org/10.21037/atm.2020.03.76

Adderley reviewed studies of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKI) plus anti-angiogenesis inhibitors for *EGFR*-mutated lung cancer and focused on the importance of overall survival (OS) data from the NEJ026 study (1). Horinouchi, in his review, outlined the position of using a combination of EGFR-TKI and chemotherapy in standard treatment for *EGFR*-mutated tumors (2).

A combination of EGFR-TKI plus an anti-angiogenesis inhibitor is promising treatment for patients with *EGFR*-mutated tumors. Recently, another phase III study, the RELAY study that involved a combination of erlotinib and ramucirumab, showed longer progression-free survival [PFS; 19.4 *vs.* 12.4 months, hazards ratio (HR) 0.591; 95% confidence interval (CI): 0.461–0.760; P<0.001] (3). Because an effect was not observed after the addition of bevacizumab for a subgroup with brain metastasis in the NEJ026 study, it is thought that the PFS of the RELAY study, excluding brain metastasis, was comparable to the PFS result from our NEJ026 study (16.9 *vs.* 13.3 months, HR 0.605, 95% CI: 0.417–0.878; P=0.016) (4). A combination of EGFR-TKI plus an anti-angiogenesis inhibitor yielded consistently longer PFS data in these two studies, and also in a JO25567 phase II study (16.0 *vs.* 9.7 months, HR 0.54, 95% CI: 0.36–0.79; P=0.0015) (5). The three studies also demonstrated an effect on tumors with an L858R subtype, which respond poorly to EGFR-TKI monotherapy compared to tumors with an exon 19 deletion.

Osimertinib monotherapy has been approved as first-line treatment for lung cancer with an *EGFR* mutation in Japan. The first priority of first-line treatment for this disease became osimertinib monotherapy. Recently, updated OS data for an Asian subgroup in the FLAURA study was reported in ESMO. In the Asian subgroup, osimertinib did not yield an OS benefit and the Kaplan-Meier curve for OS was crossed at 40 months (HR 0.995, 95% CI: 0.752–1.319). This data encourages the development of combination treatment due to achieving longer OS as a substitute for first-line osimertinib treatment. In a L858R mutation subgroup, osimertinib was not superior to first generation EGFR-TKI (HR 0.996, 95% CI: 0.708–1.404). A combination of erlotinib and an anti-angiogenic inhibitor, equally active for the L858R mutation as well as the exon 19 deletion, is considered a promising candidate for the treatment of tumors with an L858R mutation. When osimertinib use as a second or more line of TKI treatment, osimertinib is usable just after the detection of a T790M mutation in Japan. In this situation, we need to understand whether T790M-resistant mutations occur with the same frequency in combination treatment with EGFR-TKI and an

anti-angiogenesis inhibitor as in EGFR-TKI monotherapy. Although the BELIEF study described how a combination of erlotinib plus bevacizumab showed more efficacy in *de novo* T790M tumors compared to T790M negative tumors (6), both NEJ026 and RELAY studies showed the same frequency of T790M mutations after the failure of combination treatments compared to erlotinib monotherapy. This result implied that sequential osimertinib treatment may achieve longer OS by the prolongation of EGFR-TKI treatment after the emergence of T790M mutations.

We have now collected and are currently analyzing OS data from NEJ026. We hope to be able to present this information at major international conferences this year.

Acknowledgments

Funding: None.

Footnote

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm.2020.03.76). The author received lecture fees from Chugai Pharmaceutical., AstraZeneca, and Boehringer and has been supported through clinical studies by Chugai Pharmaceutical.

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.

Cite this article as: Maemondo M. Potential of combination therapy in EGFR mutated lung cancer. Ann Transl Med 2020;8(7):518. doi: 10.21037/atm.2020.03.76

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