Letter to the Editor

Treatment failure patterns of adjuvant gefitinib therapy and minimal residual disease detection in resected EGFR-mutant non-small cell lung cancer: author's reply

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We appreciate the remarks on our recent ADJUVANT publication of comparing spatial and temporal recurrence patterns between gefitinib and VP (vinorelbine plus cisplatin) chemotherapy in selected stage II–IIIA NSCLC patients with activating EGFR mutations. The recurrent model is very important for early non-small cell lung cancer (NSCLC) treated with curative procedure that could guide making future treatment strategy to cure disease. In our manuscript we built a new analytical method based on hazard ratios that showed the unique spatial-temporal recurrent patterns. In gefitinib group, we observed that recurrence risk increased at a constant rate 12 months post-surgery. It could be inferred that gefitinib could not kill tumor cells in these patients. The highest peak occurred at 30 months post-surgery. All of these indicated adjuvant EGFR TKI prolongs and reduces the recurrence or metastasis at space and timing for completely resected N1–N2 NSCLC (1).

Dr. Masago and colleagues pointed out that the observation period was relatively short. The primary endpoint of ADJUVANT was the comparison of DFS between gefitinib and VP therapy. Previous studies have demonstrated that median DFS was 12.2 months for N2 disease, and 19–21 months for N1 disease in the setting of adjuvant chemotherapy (2,3). Thus, we supposed the duration of 24 months for gefitinib was appropriate and the median follow-up of 36.5 months in this study would be long enough to discover the difference between the two arms. As a matter of fact, gefitinib showed a significantly longer median DFS compared with VP chemotherapy (28.7 *vs.* 18.0 months, HR =0.60, 95% CI: 0.42–0.87, P=0.005). In addition, patients in ADJUVANT trial are still during follow-up, updated survival data might be released in the future.

Masago *et al.* commented that the modified intention-to-treat (mITT) population conducted in the study has resulted in a biased cohort. The mITT population comprised randomized patients who received at least one dose of study medication and had no major protocol deviations. The ITT analysis included follow-up data of all randomized patients, intervention was the only difference between the treatment and control groups, which provided an unbiased comparison of outcomes. However, it is obviously unreasonable to treat individuals who did not receive any intervention as subjects in the analysis. Thus, we used mITT population in our study to exclude patients who did not receive any medications, which also approaches the practical situation that the adherence and completion of targeted therapy is higher than VP chemotherapy. While mITT analysis may lead to a bias, the results of the two analytical methods

ought to be presented in the study report simultaneously and reach the consistent conclusion. The main report of ADJUVANT trial published in Lancet Oncology met its primary endpoint showing significantly longer DFS with gefitinib therapy compared with VP chemotherapy both in ITT (28.7 *vs.* 18.0 months; HR =0.60, 95% CI =0.42–0.87; P=0.0054) and mITT (28.7 *vs.* 19.3 months; HR =0.70, 95% CI =0.49–0.99; P=0.044) population, which from one side supports the reliability of the mITT analysis (4). In addition, poorer DFS rates compared with other trials resulted from the different inclusion criteria, and direct numerical comparison is not appropriate. ADJUVANT trial included more patients with N2 disease (66.3%). Only 15.7% and 28% stage III patients were included in RADIANT and SELECT trial, respectively (5,6).

Masago *et al.* raised concern about the influence of T790M mutation on the treatment strategy, since the first generation EGFR TKIs are not applicable in patients with positive T790M mutation. ADJUVANT trial was not set to examine the T790M mutation, thus T790M mutation status was not available to guide EGFR TKI therapy. The results would be more accurate if patients with T790M primary resistance were excluded. Notably, EGFR T790M mutations are rarely identified in lung tumors before exposure to EGFR TKIs. Yu *et al.* identified 2,744 patients with lung cancers and only 11 (0.5%) tumor samples were identified to have baseline EGFR T790M mutations, amounting to 2% of EGFR-mutant tumors (7). The third generation EGFR TKI osimertinib in AUDURA trial might shed some new light for adjuvant targeted therapy of lung tumors with EGFR T790M mutations.

Minimal residual disease (MRD) detection after surgical resection would allow clinicians to evaluate tumor burden and tailor adjuvant therapies. However, MRD is not the focus of this follow-up imaging study, nor could it be effective to make precise conclusion of MRD clearance and clinical application only through prediction of recurrence risk. We fully agree with Dr. Masago and colleagues that multiple concerns remained limit the ability of ctDNA in determining MRD, including the appropriate commercial kit for collecting ctDNA and procedures for detecting MRD. In addition, mutations in plasma samples have not been fully concordant with those found in tumor tissues; and the presence of cfDNA could introduce false-positive findings (8). Thus, there is no generally accepted method of liquid biopsy and ctDNA negative is not equal to MRD negative currently. Applications of MRD need to be evaluated more comprehensively in prospective trials. Future MRD detection might have the potential to influence the treatment alternatives by identifying subsets of patients receiving adjuvant therapy or having further therapy withheld based on the ctDNA level.

Masago *et al.* proposed that imaging evaluation period would be better set to once every two months in protocol. We disagree with this point. Several NSCLC guidelines (NCCN, ESMO) for post-operative follow-up recommended that imaging examinations should be performed every six months for the first few years and then annually. Chest CT scan every 3–6 months for first 3 years was only recommended for stage I-II patients treated with radiotherapy primarily or stage III or oligometastatic stage IV patients treated with definitive intent in NCCN guideline. The frequency of 3-month imaging monitoring combined with symptoms based examinations in ADJUVANT trial was already higher than that recommended in guidelines and adopted in other clinical trials (e.g., SELECT: every 6 months in the first 3 years, then annually to the first 5 years) (6). Shorter surveillance intervals might provide more accurate temporal hazard rates for risk curves, while high frequency surveillance pattern is detrimental for patients, and the clinical significance is little considering current risk curves already displayed the essential recurrence peaks.

Finally, we thank Dr. Masago and colleagues for the comments on MRD detection and suggestion for prolonged follow-up. The work is ongoing and will be published in the near future.

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Footnote

Conflicts of Interest: WZZ serves as the unpaid Associate Editor-in-Chief of *TLCR*. YLW serves as the unpaid Honorary Editor-in-Chief of *TLCR*. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are 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.

References

1. Xu ST, Xi JJ, Zhong WZ, et al. The Unique Spatial-Temporal Treatment Failure Patterns of Adjuvant Gefitinib Therapy: A Post Hoc Analysis of the ADJUVANT Trial (CTONG 1104). J Thorac Oncol 2019;14:503-12.
2. Baba T, Uramoto H, Kuwata T, et al. Survival impact of node zone classification in resected pathological N2 non-small cell lung cancer. Interact Cardiovasc Thorac Surg 2012;14:760-4.
3. Andre F, Grunenwald D, Pignon JP, et al. Survival of patients with resected N2 non-small-cell lung cancer: evidence for a subclassification and implications. J Clin Oncol 2000;18:2981-9.
4. Zhong WZ, Wang Q, Mao WM, et al. Gefitinib versus vinorelbine plus cisplatin as adjuvant treatment for stage II-IIIA (N1-N2) EGFR-mutant NSCLC (ADJUVANT/CTONG1104): a randomised, open-label, phase 3 study. Lancet Oncol 2018;19:139-48.
5. Kelly K, Altorki NK, Eberhardt WE, et al. Adjuvant Erlotinib Versus Placebo in Patients With Stage IB-IIIA Non-Small-Cell Lung Cancer (RADIANT): A Randomized, Double-Blind, Phase III Trial. J Clin Oncol 2015;33:4007-14.
6. Pennell NA, Neal JW, Chaft JE, et al. SELECT: A Phase II Trial of Adjuvant Erlotinib in Patients With Resected Epidermal Growth Factor Receptor-Mutant Non-Small-Cell Lung Cancer. J Clin Oncol 2019;37:97-104.
7. Yu HA, Arcila ME, Hellmann MD, et al. Poor response to erlotinib in patients with tumors containing baseline EGFR T790M mutations found by routine clinical molecular testing. Ann Oncol 2014;25:423-8.
8. Chae YK, Oh MS. Detection of Minimal Residual Disease Using ctDNA in Lung Cancer: Current Evidence and Future Directions. J Thorac Oncol 2019;14:16-24.

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