Editorial

Adjuvant EGFR-TKIs-based therapy: are we ready?

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The increasing use of computed tomography (CT) as an imaging modality coupled with the growing uptake of lung cancer screening program have enabled the medical community to diagnose lung cancer at an earlier stage (1). Surgical resection remains the cornerstone of curative treatment and the advances in surgical techniques have led to an increase in patients undergoing curative operation with favorable short-term outcome (2,3). The substantial risk for post-operative recurrence, however, necessitate the use of adjuvant platinum-based chemotherapy for selected stage IB, and all applicable stage II–IIIA non-small cell lung cancer (NSCLC) patients (4,5).

Epidermal growth factor receptor (EGFR) mutation comprises ~32% of genomic drivers in NSCLC (38.8% in Asian, 17.4% in Caucasians and 17.2% in African Americans) and this EGFR positivity appear similar across different stages of disease (34% in Stage I, 29.9% in Stage II, 33.8% in Stage III and 37.5% in Stage IV) (6). The excellent response, favorable side effect profile and ongoing discovery of newer EGFR-TKIs make them an attractive candidate as a treatment option in the adjuvant setting (7,8). Pooled analysis of data from 1,860 patients that demonstrated an improvement in 2-year disease-free survival (DFS) rate by ~50% certainly support this (9).

Theoretically, however, there exist equally reasonable arguments against EGFR-TKIs-based adjuvant therapy. For one, the rationale for adjuvant cytotoxic chemotherapy lies in its potential to eradicate minimal residual disease (MRD), and studies have shown that tumor can develop rapid cell adhesion response that sacrifices tumor growth to evade the cytotoxic effect of EGFR-TKIs (10). In such instance, the "adjuvant" EGFR-TKIs may only serve to suppress cell growth but would not be able to achieve the desired MRD eradication. Indeed, there are studies that observed rapid disease recurrence upon cessation of adjuvant EGFR-TKIs that seems to support this claim (11).

In this issue of Translational Lung Cancer Research, an international, multidisciplinary panel was established to extensively review the latest available evidence and make recommendations on this much anticipated (and debated) subject. Starting with addressing the role of routine EGFR mutations testing in all surgically resected NSCLC to stratify the risk of post-operative recurrence (12), the author introduced the concept of clinical & gene panel-based prediction models to assess such risk (13,14). Recurrence risk stratification for patients with expected poor tolerance to chemotherapy formed the basis of the current recommendation of considering EGFR-TKI (in lieu of standard platinum-based chemotherapy) as the chemotherapeutic agent for adjuvant therapy.

The author must be praised in their effort to then soldier on to answer important practical questions, including addressing the rationale and recommendation on the minimum adjuvant EGFR-TKI treatment period (2 years), whether these patients should be monitored differently during therapy (annual MRI brain and bone scan in addition to CT thorax) and the risk (or lack of) T790M induction with the use of adjuvant EGFR-TKI. The final part of the consensus statement touched upon the unfortunate issue of true recurrence and metastasis and covered the pros and cons

of using archival versus re-biopsy tissue to guide treatment (15), as well as the rationale to retry the original adjuvant EGFR-TKIs in the event of post-adjuvant recurrence (16).

The astute reader will notice that the layout of the paper consists not only of the consensus statements, but also a follow-up section that contain commentaries from invited experts in the field. This is a true testament of the evolving nature of this important issue and the dedication that is required to continue to pursue this further into the future. Notwithstanding this, however, I believe readers will find the consensus paper informative and practice changing.

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Footnote

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