Letter to the Editor

Personalized adjuvant treatment: go through the past to the future

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Provenance: This is an invited article by the Section Editor Ji-Gang Wang (Department of Pathology, The Affiliated Hospital of Qingdao University, Qingdao University, Qingdao, China).

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Klevansky M, John T. Can molecularly targeted therapy cure patients with resected EGFR mutant NSCLC? J Thorac Dis 2018;10:S1986-8.

Masago K, Fujita S, Yatabe Y. Targeting minimal residual disease after surgery with molecular targeted therapy: the real path to a cure? J Thorac Dis 2018;10:S1982-5.

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Thanks for Pro. Roviello, Klevansky and Masago for their interest in ADJUVANT study and appreciate it raises questions about the eventual OS benefits and ctDNA detection for adjuvant TKI treatment in epidermal growth factor receptor (*EGFR*) mutant patients.

Early-stage non-small cell lung cancer (NSCLC) is amenable to curative resection so that it has always been considered as a "curative disease". However for postoperative stage II–IIIA NSCLC, disease free survival (DFS) ranges from 21 months to 9 months actually (1). Furthermore 5-year overall survival (OS) is only around 40–50% which implies almost half of them cannot be cured (2). To prolong survival, postoperative adjuvant chemotherapy has been extensively studied over the past decades.

A glimpse of past

In the twentieth century chemotherapy was the cornerstone of NSCLC treatment since it was regarded as "one disease" before the discovery of driver mutations. On the basis of studies—IALT, JBR10, ANITA and finally LACE individual patients data (IPD) meta-analysis, all major guidelines subsequently recommended cisplatin-based chemotherapy after surgical resection for stage II and III NSCLC patients. However 5-year OS benefit has plateaued with limited 5% improvement along with inevitable adverse effects (3). Following the observation that tumors with oncogenic driver mutations, such as *EGFR* mutations can respond dramatically to selected targeted therapies, lung cancer management stepped into the precision era. Due to the dramatic response of EGFR-TKI in advanced NSCLC, it is reasonable to wonder whether we can extend this benefit to early stage NSCLC.

Unlike previous clinical trials, ADJUVANT was a precise study which specifically enrolled *EGFR*-mutated patients. TKI was compared with chemo head to head in N1-N2 NSCLC who had higher risky in recurrence and also more response to TKI. Under this targeted selection background, adjuvant gefitinib prolonged 10.0 months longer of DFS than chemo (4). In post-hoc analysis of long-term NSCLC recurrence, adjuvant gefitinib could also control extracranial metastasis more and postpone recurrence peak of CNS metastases (5). Due to the significantly increased DFS, diminish toxic effects, and improved HRQoL, adjuvant TKI has become a considerable option for *EGFR* mutated NSCLC with N1–N2 metastasis. At this point ADJUVANT study does bring a major breakthrough in adjuvant setting. However the profound value might be in redefining the emerging areas on postoperative treatment.

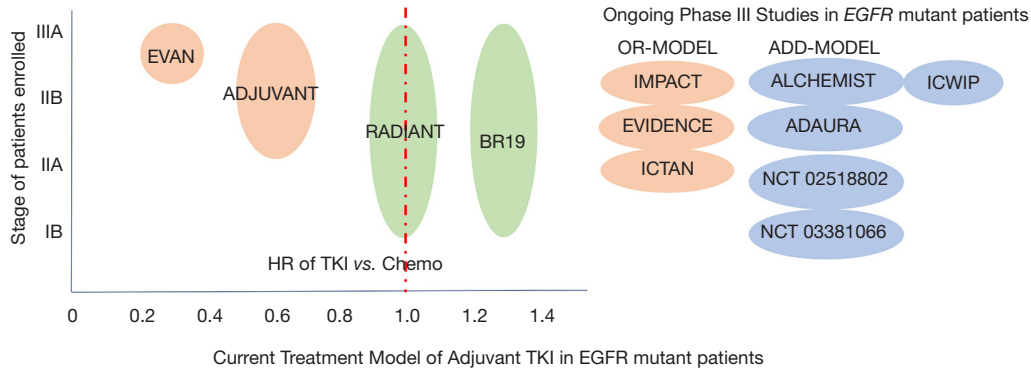

Figure 1 Current treatment model of adjuvant TKI. As for ADD model, patients were assigned to achieve plantium-based chemotherapy at first followed by EGFR-TKIs, such as BR.19, RADIANT with HR 1.2 and 0.9 respectively. For OR model, patients were randomized to receive either EGFR-TKIs or cisplatin based chemotherapy right after operation, such as EVAN, ADJUVANT with HR 0.27 and 0.61 respectively. Green plots: patients enrolled without *EGFR* mutation selected; Orange plots: patients enrolled with *EGFR* mutation selected and given by OR-MODEL; Blue plots: patients enrolled with *EGFR* mutation selected and given by ADD-MODEL.

A scan of present

Nowadays there are two models of adjuvant TKIs therapy, "ADD" and "OR". As for ADD model, patients were assigned to achieve plantium-based chemotherapy at first followed by EGFR-TKIs, such as BR.19, RADIANT, SELECT and ALCHEMIST. Under this algorithm, OS was set up as the primary endpoint since patients have received the traditional chemo plus TKI. While in ADJUVANT study, the major objective was to investigate whether EGFR-TKI might be a viable treatment alternative to chemotherapy. Patients were then randomized to receive either EGFR-TKIs or cisplatin based chemotherapy right after operation (*Figure 1*) (4,6). Therefore DFS was a rational endpoint. However due to the merged Kaplan-Meier curves of DFS and immature OS data, adjuvant gefitinib seemed like to just delay recurrence rather than to improve cure rates. Researchers then questioned adjuvant TKI might not be an effective treatment. In fact DFS could be judged as surrogate for OS in adjuvant setting since it is not confounded by crossover or subsequent treatment (7). Besides recurrent patients still have the opportunity to rechallenge TKIs and PFS could be nearly equal to that in a de novo advanced *EGFR*-mutant population. So even if mature OS data for ADJUVANT did not show a significant difference between the two options, some patients would still favor adjuvant gefitinib based on increased DFS and safety profile.

Adjuvant TKIs indeed provides an alternative option to chemotherapy for *EGFR* mutant patients. However it must also be noted that the proportion of patients with disease relapse was comparable between the two treatment groups (52% with gefitinib and 50% with vinorelbine plus cisplatin) (4). So under the context of *EGFR* mutation how could we make further efforts to precisely select population that would benefit most from adjuvant TKI? This personalized adjuvant idea is a future orientation.

A vision for the future

In addition to provide an optimal adjuvant treatment, ADJUVANT does offer insight into some unresolved questions. First of all the overall duration of benefit with gefitinib varies among patients even if all of them carried with *EGFR* mutations. This phenomenon might contribute to the intratumor heterogeneity in early-stage NSCLC. In the context of *EGFR* mutation, coexisting genetic alterations commonly occurred and cooperate with the primary driver as co-drivers which contributes to promote tumor progression and limit targeted therapy response (8). So the comprehensive understanding of genetic profile from baseline specimen might be necessary to precisely select population for either adjuvant TKI or chemo. Secondly lung cancer real adjuvant therapy is supposed to eradicate the minimal residual disease (MRD). A rapidly increasing body of work has established that ctDNA drawn after completion of curative therapies can identify patients with MRD. Technical development has made the detection available, ex. flow cytometry, digital polymerase chain reaction

(PCR) techniques or next generation sequencing (9). Along with ctDNA detection, future adjuvant trials may adopt more personalized study designs. One is to direct postoperative treatment based on ctDNA status as an adjuvant colon cancer trial has shown that serial ctDNA status might serve as a real-time marker of adjuvant therapy efficacy (10). Thus ctDNA detection would contribute to the timing and duration adjuvant TKI or chemotherapy. At this point ctDNA detection hold the promising of achieving personalized adjuvant treatment. However there are still other questions need deeper consideration, such as, what is the best timing of ctDNA detection after surgery? Can current diagnostic platforms maximize sensitivity of ctDNA detection and so on.

In summary, disease relapse highlights the need for treatment optimization in the adjuvant setting for patients with NSCLC after surgery. TKI does provide a superior option for adjuvant setting. With the diversification of treatment options, how to achieve personalized adjuvant treatment becomes the key question. So that ctDNA shows great promise in adjuvant therapy. At present we need to launch collaborative efforts involving clinicians, researchers, and technologists to incorporate novel ideas and approaches to promote the full potential of ctDNA for the betterment of our patients.

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None.

Footnote

Conflicts of Interest: The 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.

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