Science Bulletin 67 (2022) 1402–1405

Contents lists available at ScienceDirect

Science Bulletin

journal homepage: www.elsevier.com/locate/scib

News & Views

Toward a cure for lung cancer: important advances in operable non-small cell lung cancer

Si-Yang Maggie Liu [a], Guang-Ling Jie [b,c], Yi-Long Wu [b,c,*]

[a] Department of Hematology, First Affiliated Hospital, Jinan University, Guangzhou 510632, China
[b] Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou 510080, China
[c] School of Medicine, South China University of Technology, Guangzhou 510006, China

Over the past 20 years, the discovery of genes driving non-small cell lung cancer (NSCLC) has intensified; today, NSCLC is divided into driven and non-driven populations. Targeted therapy and programmed cell death-1 (PD-1) inhibitors have become the standard of care for advanced driven and non-driven NSCLC, respectively. By contrast, although the 5-year survival rate has improved by only 5%, adjuvant chemotherapy remains the standard for resected NSCLCs and no significant change has occurred in clinical practice during the past 25 years. Whether the survival advantages afforded by targeted therapy and immunotherapy for advanced NSCLC will also be evident for early or localized NSCLC remains an open question. In 2021, several trials made important advances in operable NSCLC that may pave the way toward a cure for lung cancer.

In 2017, Zhong et al. [1] firstly reported a randomized phase III clinical trial investigating the potential use of the adjuvant epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) gefitinib. Such treatment improved the median disease-free survival (DFS) from 19.8 to 30.8 months (hazard ratio [HR] = 0.56); but did not increase overall survival (OS) (75.5 vs. 62.8 months, HR = 0.92). The IMPACT trial [2], which had the same design as CTONG1104 [1], reported in 2021 that gefitinib did not improve the median DFS (35.9 vs. 25.1 months, HR = 0.92) or OS (5-year survival rate 78.0% vs. 74.6%, HR = 1.03) compared with adjuvant chemotherapy in patients with resected *EGFR*-mutant NSCLC. The EVIDENCE trial [3] explored the effects of the first-generation TKI (icotinib) and led to the approval of icotinib as an adjuvant treatment in patients with resected NSCLC with *EGFR* mutation. Compared with standard chemotherapy, icotinib showed a significant benefit in DFS (median DFS: 47.0 vs. 22.1 months, HR = 0.36, $P < 0.0001$). The ADAURA trial [4] was the first biomarker-specific adjuvant study, comparing the third-generation TKI osimertinib with placebo in patients with completely resected *EGFR* mutation-positive NSCLC. The primary endpoint (median DFS) was not reached in the osimertinib arm and was 19.6 months in the placebo arm (HR = 0.17). This encouraging result was unprecedented in adjuvant treatment for NSCLC. Although the OS data are immature, the US Food and Drug Administration (FDA) has approved osimertinib as a standard of care in adjuvant setting for patients with resected *EGFR*-mutant stage IB-IIIA NSCLC, with or without adjuvant chemotherapy. The updated American Society of Clinical Oncology (ASCO) guidelines do not recommend adjuvant chemotherapy for stage IB patients, but do for those with stage II-IIIA disease. Adjuvant osimertinib should be given to stage IB patients and should be prescribed after adjuvant chemotherapy for stage II-IIIA *EGFR*-mutant patients. If patients cannot tolerate chemotherapy, osimertinib could be given as adjuvant treatment.

The CTONG1103 trial [5] is a phase II, randomized controlled trial of erlotinib versus gemcitabine plus cisplatin as neoadjuvant and adjuvant therapy in patients with stage IIIA-N2 NSCLC with *EGFR* mutations. In the erlotinib group, the difference in the primary endpoint (ORR) did not attain statistical significance (54.1% vs. 34.3%, $P = 0.092$), and no pathological complete response (pCR) or major pathological response (MPR) was identified. This result may be attributable to the small sample size ($n = 72$) and the limited exposure to erlotinib (42 d). The median PFS of the erlotinib group exceeded that of the chemotherapy group (21.5 vs. 11.4 months, HR = 0.39, $P < 0.001$), but the OS data are immature. This was the first study to demonstrate the superior PFS afforded by erlotinib (compared with chemotherapy) in neoadjuvant and adjuvant settings of stage IIIA-N2 *EGFR*-mutant NSCLC. The clinical trial of osimertinib as neoadjuvant therapy with or without chemotherapy is already recruiting participants.

Recently, the US FDA approved the first PD-L1 inhibitor, atezolizumab, as adjuvant treatment for stage II-IIIA NSCLC, following complete resection of PD-L1-positive tumors, after treatment with doublet chemotherapy. The decision was based on the results of the IMpower010 trial [6] in 2021. The trial enrolled 1280 patients and results showed that the median DFS was not reached in the atezolizumab arm compared with 35.3 months in the best supportive care arm (HR = 0.66, $P = 0.004$). KEYNOTE091 [7], the randomized trial for adjuvant immunotherapy has yielded important results. In terms of the primary endpoint, adjuvant pembrolizumab improved the DFS of all patients with completely resected early-stage NSCLC, regardless of PD-L1 expression status (53.6 vs. 42.0 months, HR = 0.76, $P = 0.0014$); however, the OS data are immature.

* Corresponding author.
E-mail address: syylwu@live.cn (Y.-L. Wu).

https://doi.org/10.1016/j.scib.2022.06.008

Several clinical trials of neoadjuvant immunotherapy have reported promising results. CheckMate816 trial [8] compared nivolumab plus platinum-based chemotherapy to chemotherapy alone as neoadjuvant treatments for patients with stage IB-IIIA NSCLC. The trial met the primary endpoints, with a 24% pCR rate and median event-free survival (EFS) that improved from 20.8 to 30.1 months. On March 4, 2022, the FDA approved nivolumab combined with platinum-doublet chemotherapy for patients with resectable NSCLC in neoadjuvant setting. This was the first FDA approval of neoadjuvant therapy for early-stage NSCLC patients. Neoadjuvant immunotherapy thus became the standard of care in this setting.

Pathological evaluation is very important for assessing treatment response and predicting prognosis. The pathologic response can serve as a surrogate endpoint. The MPR and pCR rates have already been set as primary endpoints in neoadjuvant clinical trials in resectable NSCLC (Table S1 online). However, it is not clear whether MPR or pCR can reflect a survival benefit. The CheckMate 816 trial reported that in patients exhibiting pCR, the HR for nivolumab plus chemotherapy (vs. chemotherapy alone) was 0.13 (95% CI 0.05–0.37), indicating that the pCR did reflect EFS in this trial. We summarized the ongoing clinical trials of adjuvant and neoadjuvant targeted therapy and immunotherapy for NSCLC patients (Table S1 online).

In general, OS is an objective and indisputable endpoint for evaluating treatment modality. The LACE meta-analysis constitutes a landmark for traditional adjuvant chemotherapy; it involves 4584 patients from five different clinical trials [9]. The overall HR of death was 0.89 (95% CI 0.82–0.96) and HR for DFS was 0.84 (0.78–0.91), corresponding to a 5-year absolute benefit of 5.4% for chemotherapy. Most adjuvant clinical trials have selected DFS as a primary endpoint. We performed a pooled analysis on 1697 patients from seven different randomized clinical trials of adjuvant targeted therapy. The HR for DFS was 0.44 (95% CI 0.38–0.52) and HR for OS was 0.94 (95% CI 0.72–1.22) (Fig. 1). The DFS benefit did not translate to OS benefit when a first-generation TKI was used as an adjuvant treatment. Interestingly, investigations into adjuvant chemotherapy required a large patient population to discern any small significant difference (HR = 0.84) whereas investigations into adjuvant EGFR-TKIs only required a small number of patients to identify major improvements (HR = 0.44). By combining the evidence from both adjuvant chemotherapy and EGFR-TKIs trials, the OS trend of resected NSCLC has improved in the last 10 years. The 5-year survival rate was 53.2% to 84.8% in adjuvant targeted treatment for N1 to N2 patients, compared with 38% (N2) and 50% (N1) in the IASLC database. With the emergence of more effective treatments, DFS is becoming a vital endpoint of clinical trials in an adjuvant setting [10].

Results provided from clinical trials using EGFR-TKIs in adjuvant setting have led to new questions concerning the role of adjuvant chemotherapy in *EGFR* mutant resected NSCLC. However, most studies have used DFS as primary endpoint and OS as secondary endpoint. Therefore, it is difficult to state that chemotherapy can be replaced by EGFR-TKI. The ADAURA trial [11] was designed to compare osimertinib and placebo after adjuvant chemotherapy. Results showed that only 60% of patients received adjuvant chemotherapy. This is broadly in line with the results of previous studies and current clinical practice. The HR values were 0.16 in the adjuvant chemotherapy and 0.23 in the non-chemotherapy groups. The DFS improvement afforded by osimertinib was not dependent on chemotherapy. Another trial, ICAN [12], was a non-interventional, real-world study; the results suggested that adjuvant chemotherapy did not improve survival outcomes regardless of *EGFR* mutation status and postoperative stage. Taken together, these studies were not specifically designed to evaluate the role of adjuvant chemotherapy in *EGFR* mutant patients and the results cannot determine whether adjuvant chemotherapy is unnecessary. Thus, adjuvant chemotherapy is still the standard of care in resected NSCLC. Future studies to explore the role of adjuvant chemotherapy in resected *EGFR* mutant NSCLC are required.

The extended use of next-generation sequencing has contributed to the refinement of the *EGFR* mutant patients subgroup. In the CTONG1104 trial [1], five biomarkers were selected to be components of the MINERVA score (*TP53* exon 4/5 mutations, *RB1* alteration, copy number gains of *NKX2-1*, *CDK4*, and *MYC*) due to their distinct benefit in adjuvant therapy [13]. Of the total number of cases, 35% (60/171) were highly TKI-preferable (HTP), 51% (87/171) were TKI-preferable (TP), and 14% (24/171) were chemo-preferable (CP). The score showed that patients with an *RB1* alteration would benefit from adjuvant chemotherapy even with *EGFR* mutation. The 5-year survival rate was 61.5% (HR = 2.47, 95% CI 0.76–8.02). In patients with a MINERVA score of less than −0.5 (HTP subgroup), gefitinib led to significantly longer DFS and OS. And the 5-year OS rate was 67% in HTP subgroup that received gefitinib (HR = 0.43, 95% CI 0.21–0.88). This exploratory, retrospective analysis of the CTONG 1104 trial has unraveled the interplay between genetic constructs of *EGFR* co-mutations and clinical outcomes in stage II-III resected NSCLC to aid the adjuvant paradigm. The MINERVA score presents a fresh perspective for future studies to guide the development of more personalized adjuvant therapies, and their transition from bench to bedside.

Based on the CTONG 1104 biomarker analysis, we found that the efficacy of adjuvant gefitinib may be associated with the local tumor immune microenvironment and antitumor T cell responses that could be characterized by the distribution and diversity of T cell receptors (TCRs) [14]. Low-risk patients had a significantly longer OS (5-year survival rate 79%, HR = 0.27, 95% CI 0.53–0.57, $P < 0.001$) and PFS (2-year DFS rate 71%, HR = 0.50, 95% CI 0.29–0.86, $P = 0.011$). This may provide a novel perspective for adjuvant treatment, for resectable NSCLC. These results provide support for the hypothesis that the special TCR rearrangement status of infiltrated T cells in tumors may directly influence the efficacy of treatment. Specific TCR profiles may therefore be used for the selection of patients with *EGFR* mutation who could benefit from checkpoint blockade treatment.

Minimal residual disease (MRD) is a new concept in solid tumors. In general, MRD is used in the context of completely curative intent for solid tumors, such as lung, breast, or colon cancer. In these circumstances, "MRD positive" suggests that cancers persist and will relapse. Alternatively, "MRD negative" suggests that the cancer may have been cured and there is no need for any additional treatment. Some retrospective studies have confirmed these findings. In 2017, Chaudhuri et al. [15] used cancer personalized profiling by deep sequencing (CAPP-Seq) assay to detect the ctDNA for the evaluation of MRD status in patients who received curative surgery or radiotherapy (with or without chemotherapy). The results showed that 17 patients with undetectable MRD survived 36 months without any disease relapse, and that 20 patients with detectable MRD experienced cancer recurrence, although effective treatment could delay disease relapse. In 2022, Zhang et al. [16] identified a subpopulation of localized NSCLC cases with longitudinal undetectable MRD, with only 3.2% of patients recurred, indicating that the potentially cured patients were almost identified. Based on these results, some validated phase III clinical trials are now ongoing. MERMAID-1 and MERMAID-2 are two phase III trials investigating the checkpoint inhibitor, durvalumab, and its randomized use in patients who are MRD positive. FATES-CTONG 2105 focuses on *EGFR* mutant patients with complete resection, where MRD negative patients do not receive treatment; if patients become MRD positive during follow-up, they receive EGFR-TKI

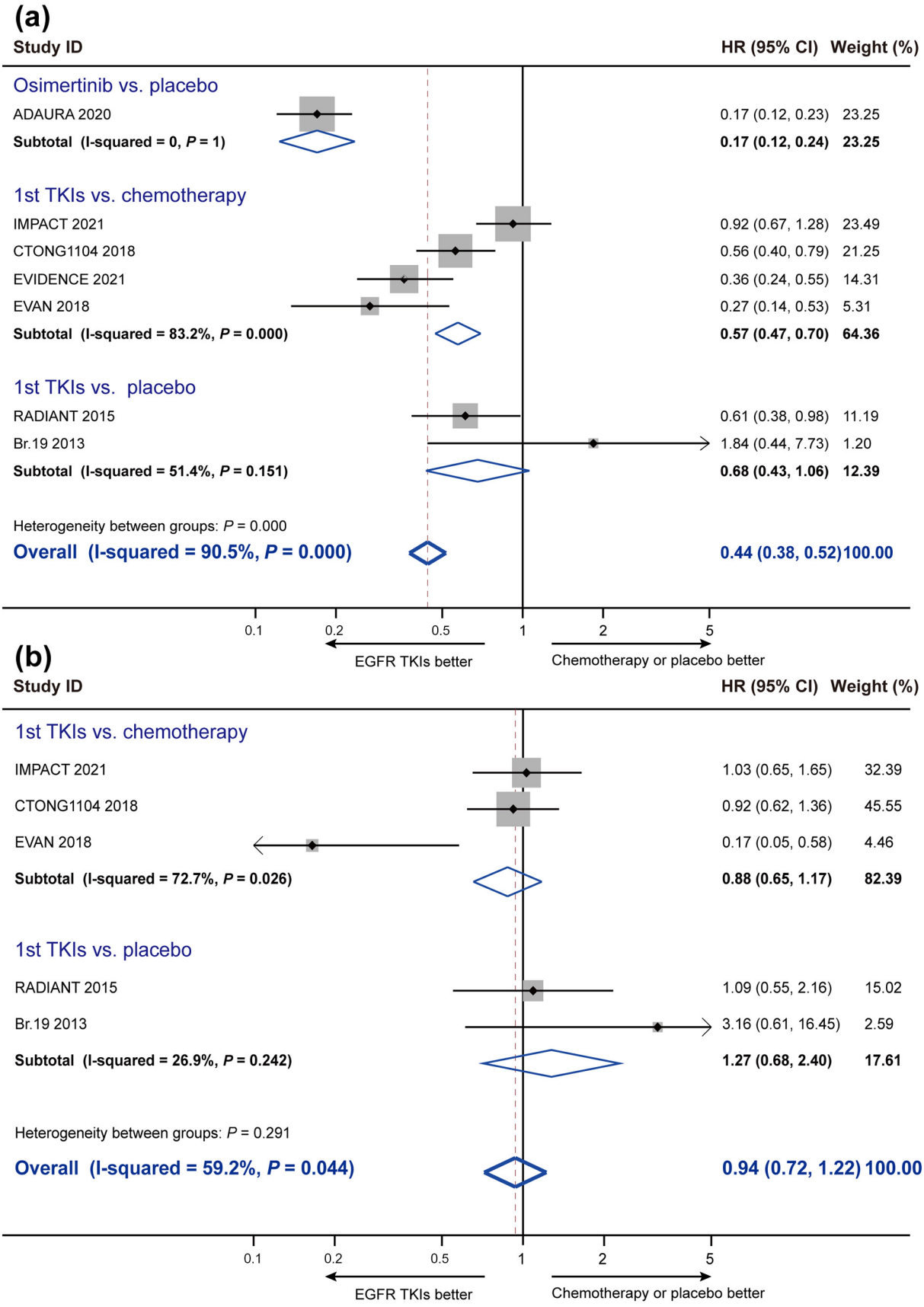

Fig. 1. (Color online) Pooled analysis of (a) seven randomized clinical trials of adjuvant targeted therapy evaluating the hazard ratio (HR) for disease-free survival (DFS) and (b) the HR for overall survival (OS) in five trials.

treatment. In the future, the results of these trials will identify which subgroup of patients after complete resection can be classed as "cured" and which require additional treatment.

Several promising therapeutic approaches have also emerged. Antibody-drug conjugates (ADCs) are a new class of anti-cancer therapies, that target *HER2*, *HER3*, or *TROP2*, and have shown promising efficacy in lung cancer. Preclinical results have indicated that ADCs enhanced sensitivity to PD-1/PD-L1 inhibitors via stimulation of dendritic cells; this combination therapy may both overcome resistance and enhance efficacy. ADCs are cytotoxic drugs with defined targets; their high response rates make it possible to facilitate the future application of this combination with checkpoint inhibitors in the perioperative setting. CT-0508, a HER2-directed chimeric antigen receptor macrophage (CAR-M), was granted Fast Track designation by the US FDA in September 2021 based on its early results. The first-in-human study results were recently released (in 2020) by the ASCO. CT-0508 was successfully produced from 7 patients with solid tumors and there were no safety concerns [17]. Theoretically, PD-1/PD-L1 inhibitors combined with chimeric antigens receptor (CAR) T-cell therapy would greatly benefit patients with solid tumors. Proof of concept for the safety and efficacy of CAR T-cells in solid tumors is still pending. Challenges include the unknown migration of CAR T-cells and maintaining their viability and function within the tumor microenvironment. Theoretically, cell therapy is appropriate when the tumor burden has been minimized. Currently, adjuvant checkpoint blockade has been used successfully to treat patients with resected NSCLC; this, combined with cell therapy (such as CAR-macrophage (CAR M)- or CAR-nature killer (CAR NK)-cell therapy), may become important in anti-tumor therapies in the future.

In conclusion, NSCLC treatments are undergoing great changes with the rapid progress of evidence-based medicine and precision medicine. Multiple perioperative treatments are improving long-term patient survival. This is a step in the right direction toward curing lung cancer by utilizing new treatment options and new approaches.

Conflict of interest

Yi-Long Wu reports consulting and advisory services and declares speaker fees for Roche, AstraZeneca, Eli Lilly, Boehringer Ingelheim, Sanofi, Merck Sharp & Dohme, and Bristol Myers Squibb. All other authors declare that they have no conflict of interest.

Acknowledgments

This work was supported by the Key Lab System Project of Guangdong Science and Technology Department, Guangdong Provincial Key Lab of Translational Medicine in Lung Cancer (2017B030314120), Guangdong Provincial People's Hospital Scientific Research Funds for Leading Medical Talents in Guangdong Province (KJ012019426), and China Postdoctoral Science Foundation (2021M701422).

Appendix A. Supplementary materials

Supplementary materials to this article can be found online at https://doi.org/10.1016/j.scib.2022.06.008.

References

[1] 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: final overall survival analysis of CTONG1104 phase III trial. J Clin Oncol 2021;39:713–22.
[2] Tada H, Mitsudomi T, Misumi T, et al. Randomized phase III study of gefitinib versus cisplatin plus vinorelbine for patients with resected stage II-IIIA non-small-cell lung cancer with EGFR mutation (IMPACT). J Clin Oncol 2022;40:231–41.
[3] He J, Su C, Liang W, et al. Icotinib versus chemotherapy as adjuvant treatment for stage II-IIIA EGFR-mutant non-small-cell lung cancer (EVIDENCE): a randomised, open-label, phase 3 trial. Lancet Respir Med 2021;9:1021–9.
[4] Wu YL, Tsuboi M, He J, et al. Osimertinib in resected EGFR-mutated non-small-cell lung cancer. N Engl J Med 2020;383:1711–23.
[5] Zhong WZ, Chen KN, Chen C, et al. Erlotinib versus gemcitabine plus cisplatin as neoadjuvant treatment of stage IIIA-N2 EGFR-mutant non-small-cell lung cancer (EMERGING-CTONG 1103): a randomized phase II study. J Clin Oncol 2019;37:2235–45.
[6] Felip E, Altorki N, Zhou C, et al. Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB-IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase 3 trial. Lancet 2021;398:1344–57.
[7] Paz-Ares L, O'Brien MER, Mauer M, et al. VP3-2022: Pembrolizumab (pembro) versus placebo for early-stage non-small cell lung cancer (NSCLC) following complete resection and adjuvant chemotherapy (chemo) when indicated: randomized, triple-blind, phase III EORTC-1416-LCG/ETOP 8-15 – PEARLS/KEYNOTE-091 study. Ann Oncol 2022;33:451–3.
[8] Forde PM, Spicer J, Lu S, et al. Neoadjuvant nivolumab plus chemotherapy in resectable lung cancer. N Engl J Med 2022;386:1973–85.
[9] Pignon JP, Tribodet H, Scagliotti GV, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. J Clin Oncol 2008;26:3552–9.
[10] Liu SY, Zhang JT, Wu YL. What we have learned from adjuvant therapy for resected EGFR-mutant non-small-cell lung cancer. J Clin Oncol 2022;40:217–20.
[11] Wu YL, John T, Grohe C, et al. Postoperative chemotherapy use and outcomes from ADAURA: osimertinib as adjuvant therapy for resected EGFR-mutated NSCLC. J Thorac Oncol 2022;17:423–33.
[12] Yang XN, Yan HH, Wang J, et al. Real-world survival outcomes based on EGFR mutation status in Chinese patients with lung adenocarcinoma after complete resection: results from the ICAN study. JTO Clin Res Rep 2022;3:100257.
[13] Liu SY, Bao H, Wang Q, et al. Genomic signatures define three subtypes of EGFR-mutant stage II-III non-small-cell lung cancer with distinct adjuvant therapy outcomes. Nat Commun 2021;12:6450.
[14] Chen C, Liu SM, Chen Y, et al. Predictive value of TCR vbeta-jbeta profile for adjuvant gefitinib in EGFR mutant NSCLC from ADJUVANT-CTONG 1104 trial. JCI Insight 2022;7:e152631.
[15] Chaudhuri AA, Chabon JJ, Lovejoy AF, et al. Early detection of molecular residual disease in localized lung cancer by circulating tumor DNA profiling. Cancer Discov 2017;7:1394–403.
[16] Zhang JT, Liu SY, Gao W, et al. Longitudinal undetectable molecular residual disease defines potentially cured population in localized non-small cell lung cancer. Cancer Discov 2022;12:1690–701.
[17] Reiss KA, Yuan Y, Barton D, et al. A phase 1, first-in-human (FIH) study of adenovirally transduced autologous macrophages engineered to contain an anti-HER2 chimeric antigen receptor (CAR) in subjects with HER2 overexpressing solid tumors. J Clin Oncol 2022;40:tps668.

Si-Yang Maggie Liu graduated from South China University of Technology in 2021. She is currently a postdoc at Department of Hematology, First Affiliated Hospital, Jinan University. Her current research focuses on predictive biomarkers, and checkpoint blockade therapy in perioperative and advanced-stage non-small-cell lung cancer settings.

Yi-Long Wu is the President of Guangdong Medical Doctors Association, Chief Expert of Guangdong Provincial People's Hospital, Honorary Director of Guangdong Province Lung Cancer Research Institute, Chair of China Thoracic Oncology Group, and President of the World Conference on Lung Cancer (WCLC) 2020. His study interest is the development of evidence-based medicine and precision medicine for lung cancer patients.