

Targeting minimal residual disease after surgery with molecular targeted therapy: the real path to a cure?

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Stage II–IIIa non-small cell lung cancer (NSCLC) affects a highly heterogeneous group of patients with differences in the extent and localization of the disease, and the definition of stage II–IIIa disease has changed over time. The 5-year survival for completely resected stage II–IIIa NSCLC patients is poor (36–60%) (1). Indeed, at least one-third of patients show recurrences after surgery.

Clinical trials of adjuvant chemotherapy have been conducted to lower the recurrence rate and improve the prognosis by targeting minimal residual disease (MRD), which is considered a factor of relapse. A meta-analysis by the NSCLC collaborative group in 1995 revealed that postoperative adjuvant chemotherapy showed a 5% improvement in the 5-year survival rate (2). A meta-analysis (LACE) including five studies [ALPI (3), BLT (4), IALT (5), JBR 10 (6), ANITA (7)] comparing surgery alone and cisplatin (CDDP)-based chemotherapy showed a significant improvement in the 5-year survival rate, and the survival effect was particularly observed at stage II–IIIa in the subgroup analysis (8). Among those studies, the analysis of 1,888 cases evaluated for comparison between surgery alone and vinorelbine plus CDDP showed an improvement of 5.9% in the 5-year survival rate (9). These findings suggest that adjuvant chemotherapy by using platinum-based chemotherapy (vinorelbine plus CDDP) is currently the standard of strategy for patients with completely resected stage II–IIIa NSCLC (10,11). However, 0.8% of treatment-related deaths has been reported for CDDP-based adjuvant therapy (9).

Target therapy is not indicated outside of a clinical trial as an adjuvant therapy in this setting. For patients with or without driver mutations, the use of adjuvant target therapy including cetuximab, erlotinib and crizotinib is under evaluation (*Table 1*), and preliminary results have not suggested a survival benefit (13,14). Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) are the recommended first-line treatments for EGFR-mutant advanced NSCLC. There is implicit evidence that particularly NSCLC patients harboring *EGFR* activating mutations at resected IIIa N2 stage have a superior recurrent-free survival with erlotinib. However, whether this evidence is applied to an improvement in overall survival or merely delays recurrence remains unknown (15). Evidence is also scarce for EGFR-TKIs as adjuvant therapies for EGFR-mutant completely resected stage II–IIIa NSCLC patients. The BR 19 study retrospectively assessed the adjuvant gefitinib in genotype-nonspecific patients with completely resected stage IB–IIIa NSCLC, and no survival benefit was reported in the gefitinib-treated group (16). Two prospective trials [RADIANT (15) and SELECT (17)] showed promising survival benefit in patients with EGFR-mutant stage I–III NSCLC who received the adjuvant erlotinib. In the SELECT phase II trial (17), the 2-year disease-free survival (DFS) is 73% at stage II and 92% at stage III and in the RADIANT phase III trial (15), among the 161 patients in the *EGFR* mutant subgroup, DFS favored erlotinib.

Zhong *et al.* initiated a randomized phase III trial

Table 1 Ongoing randomized phase III trial of an EGFR-TKIs as adjuvant treatment for patients with NSCLC harboring *EGFR* activating mutations (12)

Clinical trial	Region	Stage, planned accrual, EGFR mutation	Study design	Primary end-point
NCT02125240 (ICWIP)	China	II–IIIA, 300, ex19del and L858R	Rand. to icotinib ×2 years vs. placebo ×2 years (platinum-based chemotherapy ×4 cycles)	DFS
NCT01996098 (ICTAN)	China	II–IIIA, 300, ex19del and L858R	Rand. to icotinib ×12 months vs. icotinib ×6 months vs. observation (platinum-based chemotherapy ×4 cycles)	DFS
NCT02193282 (ALCHEMIST)	U.S.	IB (≥4 cm)–IIIA, 450, ex19del and L858R without T790M	Rand. to erlotinib ×2 years vs. placebo ×2 years (after standard adjuvant chemotherapy)	OS
NCT02201992 (ALCHEMIST)	U.S.	IB (≥4 cm)–IIIA, 378, ALK-positive	Rand. to crizotinib ×2 years vs. placebo for 2 years (after standard adjuvant chemotherapy)	OS
WJOG6401L	Japan	II–IIIA, 230, ex19del and L858R without T790M	Rand. to gefitinib ×2 years vs. cisplatin/vinorelbine ×4 cycles	5-year DFS
NCT02448797 (EVIDENCE)	China	II–IIIA, 320, ex19del and L858R	Rand. to icotinib ×2 years vs. cisplatin/vinorelbine ×4 cycles	DFS
NCT02518802	China	II–IIIA (N1, N2), 220, ex19del and L858R	Rand. to cisplatin/pemetrexed ×4 cycles + gefitinib ×2 years vs. cisplatin/pemetrexed ×4 cycles	DFS
NCT01996098 (ICTAN)	China	II–IIIA, 477, ex19del and L858R	Rand. to icotinib ×12 months vs. icotinib ×6 months vs. observation (platinum-based chemotherapy ×4 cycles)	DFS
NCT02511106 (ADAURA)	International	IB–IIIA, 700, ex19del and L858R ± other EGFR mutation*	Rand. to osimertinib ×2 years vs. placebo ×2 years (standard adjuvant chemotherapy allowed)	DFS

*, including T790M. NSCLC, non-small cell lung cancer; EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor; Rand., randomization; vs., versus; DFS, disease-free survival; OS, overall survival.

(ADJUVANT/CTONG1104) to evaluate the efficacy of gefitinib compared with that of CDDP-based chemotherapy in Chinese patients who underwent complete resection for EGFR-mutant stage II–IIIA NSCLC (18). The median DFS was significantly longer with gefitinib (28.7 months) than with vinorelbine plus CDDP (18.0 months), with reduced toxicity (no interstitial lung disease) and improved quality of life. Based on these findings, these authors concluded that the adjuvant gefitinib could be a potential therapeutic choice compared with adjuvant cytotoxic chemotherapy in these patients. As a limitation, the overall survival data, which was predefined secondary endpoint, is not mature and the 3-year DFS rate does not show a significant difference between the two groups (34% *vs.* 27%, respectively). Although DFS may be a suitably valid surrogate for overall survival in the adjuvant setting, this parameter might not prove the benefit of using EGFR-TKI as a postoperative adjuvant therapy until the survival benefit is proved after a sufficient observation period, because EGFR-TKI is expected to be used in patients receiving

CDDP-based adjuvant therapy. Next, the basis of the two-year administration period of gefitinib is uncertain, which may follow the trial design of the phase III trial to assess the utility of uracil-tegafur as adjuvant therapy for completely resected stage I lung adenocarcinoma (19). Although not observed in this ADJUVANT trial, gefitinib has a fatal complication of ILD, and there are many complications that degrade QOL, such as liver dysfunction and skin rash when compared to uracil-tegafur. There is no criterion to judge whether the 2-year dosing period of gefitinib is long, short or appropriate, and it is also necessary to consider the risk of disease flare particular to EGFR-TKI after gefitinib discontinuation (20).

Despite the initial improvement in patients with *EGFR* mutant who received EGFR-TKIs, acquired resistance was observed in almost all cases. Although many resistance mechanisms have been elucidated, the *EGFR* T790M mutation in exon 20 accounts for about 50% of all acquired resistance, making testing for this alteration a key factor in determining treatment strategies using second- and

third-generation EGFR-TKIs (21,22). However, in this ADJUVANT trial, the EGFR T790M status of patients who received gefitinib as adjuvant therapy and relapsed after surgery is unknown. Thus, it may be necessary to compare gefitinib adjuvant therapy in patients who received CDDP-based adjuvant therapy and apply EGFR-TKI at the time of relapse to ascertain the influence of T790M on the treatment strategy of the ADJUVANT trial. Additionally, considering that osimertinib showed better efficacy than gefitinib and erlotinib in the first-line treatment of *EGFR* mutant advanced NSCLC, with a similar safety profile and lower rates of serious adverse events in the FLAURA trial (23), is also likely that other EGFR-TKIs including osimertinib, are better for EGFR-TKI in an adjuvant setting (12).

The strongest evidence that the treatment of MRD can prevent relapse as a measurable surrogate for cure comes from the experience of treating completely resected NSCLC patients by using adjuvant therapy, which is fundamentally intended to eradicate MRD not resected with surgical modalities (6). However, not all MRD cells seem to contribute to a disease recurrence, so the term MRD is somewhat nonspecific (24). Thus, it remains unclear whether MRD lower than the minimum detectable threshold indicates a cure. In a preoperative setting, CDDP-based therapy confers response rates that are superior to the rates achieved in advanced NSCLC (25), which may reflect the fact that early stage and advanced stage tumor cells are fundamentally different in susceptibility to chemotherapy. However, since chemotherapy does not fundamentally indicate total cell kill in the treatment of epithelial tumors, whether EGFR-TKI intervention should be performed in an adjuvant setting or at the time of relapse remains a problem. In the case of other driver mutations, such as *ALK*, *ROS1*, *RET*, *NTRK* rearrangement and the *BRAF* mutation, the usefulness of molecular targeted therapy as adjuvant treatment should also be examined.

Zhong and colleagues showed that adjuvant gefitinib led to 28.7 months [95% confidence interval (CI), 24.9–32.5] of DFS, compared with 18.0 months (95% CI, 13.6–22.3) with vinorelbine plus CDDP in patients with completely resected stage II–IIIA EGFR-mutant NSCLC. Based on this result, it is possible to apply gefitinib as standard therapy of an adjuvant therapy; however, considering the unknown influence of T790M and a fatal complication ILD, it is necessary to ascertain the appropriate timing of intervention and confirm whether targeting MRD with molecular targeted therapy is the real path to a cure.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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