Editorial

Adjuvant treatment for EGFR-mutated non-small cell lung cancer: do we have a major breakthrough?

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Zhong *et al.* reported the results of the ADJUVANT/CTONG1104 study (1), a randomized open-label phase III trial enrolling 483 Chinese patients with completely resected (R0) stage II–IIIA (N1-N2) non-small cell lung cancer (NSCLC) and epidermal growth factor receptor (EGFR)-mutant (defined as exon 19 deletion or exon 21 Leu858Arg) to receive 4 cycles of standard adjuvant Cisplatin and Vinorelbine or 24 months of the EGFR-tyrosine kinase inhibitor (TKI), gefitinib. The primary endpoint was disease free survival (DFS). Secondary endpoints included overall survival (OS), 3-year DFS, 5-year DFS, and 5-year OS, safety, tolerability and quality of life. From the initial screening of 483 patients, 222 (45.9%) were eligible and randomly assigned to standard chemotherapy or experimental arm. At a median follow-up of 36.5 months, the median DFS was significantly longer in the gefitinib arm than in chemotherapy arm (28.7 *vs.* 18.8 months; HR 0.6; 95% CI, 0.42–0.87; P=0.0054). Among secondary endpoints, OS data were not mature and, thus, not reported; 3-year DFS favored the gefitinib group and a reduced toxicity with improvement in quality of life was observed with adjuvant gefitinib compared to chemotherapy. Particularly, the most commonly reported grade 3 or worse adverse events were raised alanine and aspartate aminotransferase in the gefitinib group, neutropenia, leucopenia and vomiting in the chemotherapy group, which were absent in gefitinib arm. Serious adverse events were reported in 7 (7%) patients who received gefitinib and 20 (23%) patients who received vinorelbine plus cisplatin. The authors concluded that adjuvant gefitinib could be considered as a treatment option for selected patients with EGFR-mutated NSCLC (1).

To date, 20–25% of patients affected by NSCLC are candidates to radical surgery, but a substantial percentage of them subsequently relapse and die of their disease. Several studies and meta-analyses have confirmed the role of cisplatin-based adjuvant chemotherapy as the standard of care for patients with resected stage II–IIIA NSCLC, irrespectively of any tumour mutational status (2,3). Particularly, two trials (ANITA and North American Intergroup Trial) highlighted the role of vinorelbine in addiction to cisplatin as adjuvant treatment for stage IB, II and IIIA NSCLC (4,5). Unfortunately, the addition of post-surgery chemotherapy in this population resulted into an absolute 4–5% improvement in OS at 5 years (6,7), this resulting in still disappointing 5-year survival rates for stage II–IIIA NSCLC patients. Therefore, the improvement of outcome of adjuvant treatment represents a challenge in the management of radically resected NSCLC and, at present, no targeted therapy showed to improve survival when added to standard adjuvant chemotherapy in a randomized phase III trial. For example, the addition of the antiangiogenic

agent, bevacizumab to adjuvant chemotherapy did not improve the outcome of patients with surgically resected early-stage NSCLC in the E1505 trial (5).

The first druggable abnormalities discovered in lung cancer are EGFR tyrosine kinase mutations that occur in approximately 10% of advanced NSCLC Western patients and in 30% of Asiatic patients. In the era of precision medicine, EGFR tyrosine kinase inhibitors (i.e., gefitinib, erlotinib, afatinib, icotinib, dacomitinib and, recently, osimertinib) have become the standard first-line treatment for NSCLC patients harbouring those specific mutations (8-12). Despite this, evidences supporting EGFR-TKIs as adjuvant treatment of EGFR-mutant early stage NSCLC are still scant and controversial. Recently, two retrospective analyses (13,14) and two prospective trials (15,16) showed promising results in improving DFS in EGFR-mutant stage I–III NSCLC patients who received adjuvant EGFR TKIs compared to who did not, and, collectively, this suggests a potential OS benefit for those patients (*Table 1*).

The ADJUVANT trial is the first head-to-head trial showing a superior DFS of targeted therapy *vs.* an adjuvant standard chemotherapy in a selected population of patients with radically resected EGFR-mutant NSCLCs with a high risk of recurrence (only N1 and N2 stage disease excluding stage IB). While this represents a pivotal result for NSCLC research field, it is important to note that this trial presents some limitations. First, as underlined by the authors, the OS data are still not available and, in the intention to treat (ITT) population, the Kaplan-Meier curves for DFS separated around 12 months and then came together to about 36 months, suggesting that gefitinib maintained its clinical benefit for more than 10 months after stopping treatment at 24 months. Similar Kaplan-Meier curves were previously reported in a study of erlotinib versus placebo for NSCLC (RADIANT study) (15) and these authors concluded that EGFR-TKIs might not be curative as adjuvant treatment for patients with resected NSCLC, but rather provide clinical benefit for most patients delaying disease recurrence by roughly 10 months compared to chemotherapy. Although these data suggest that the benefit in favor of targeted therapy is clinically significant in patients properly selected based on the presence of an EGFR mutation, and that an EGFR-TKI may replace standard adjuvant chemotherapy, it is important to underline that lack of OS data is a major concern in the perspective to change current clinical practice in this specific setting. In fact, the aim of an adjuvant treatment is to eradicate the microscopic residual disease leading to the improvement in OS rather than DFS. The evidence that an EGFR-TKI could delay disease recurrence in high-risk NSCLC patients compared to standard chemotherapy is clinically relevant, but not sufficient to allow its wide use as adjuvant agent. Indeed, it is still unclear whether patients who do not receive up-front adjuvant targeted therapy may obtain an equal benefit by receiving it at disease recurrence. In addition, the median follow-up of 36.5 months seems not adequate enough considering the observed OS of 65.7 months in the ANITA trial and 85.8 months for control arm in the E1505 trial (4,5). For this reason, a longer follow-up with more mature data is awaited for definitive conclusions. In this setting, the ongoing ALCHEMIST study (NCT02201992), that is investigating adjuvant EGFR and ALK tyrosine kinase inhibitors in EGFR-mutant and ALK-positive NSCLC with a primary endpoint of OS may add important information.

Patients with IB NSCLC were not enrolled in the ADJUVANT trial. Stage I NSCLC is diagnosed in approximately 16% of all lung cancer cases (18) and the use of adjuvant chemotherapy showed improvement of OS for patients with tumors larger than 4 cm. Consequently, there is a strong rationale to investigate adjuvant EGFR TKIs also in IB EGFR-mutated NSCLC. In addition, another point to consider is that ADJUVANT trial recruited only Chinese patients, even though it is well known that the frequency of EGFR mutations is approximately 10% in Caucasian patients and up to 50% in Asian patients (19). This discrepancy may open some doubts about the reproducibility of data from ADJUVANT trial in a non-Asian NSCLC setting and, thus, will require additional investigations in this subgroup of patients. On the other hand, a confirmatory trial in Western population is likely to meet a more difficult enrolment of patients due to the lower percentage of EGFR-mutant NSCLCs. Finally, the low percentage of dose reductions (11%), discontinuation for drug-related toxic effects (3%) and adverse events of grade 3 or higher (12%) in the gefitinib arm of ADJUVANT trial may suggest the possibility of further studies with a longer duration of the EGFR-TKIs. However, it should be pointed out that most of available data on the activity of different EGFR-TKIs given in the adjuvant setting concomitantly or after standard chemotherapy derive from studies with a treatment duration of 24 months (*Table 1*). Thus, it is still questionable whether the administration of TKIs for more than 24 months could be burdened by toxicity and could facilitate the onset of biological resistance to treatment.

In conclusion, the ADJUVANT trial is the first head-to-head study showing a statistically significant DFS activity

Table 1 Trials on different EGFR-TKIs given in the adjuvant setting concomitantly or after standard chemotherapy

Author, design	NSCLC stage	EGFR selection	Number of patients, design	EGFR mutation in treatment arm (%)	Length of exposure	Primary endpoint	Results
Zhong *et al.*, ADJUVANT phase III trial (1)	II to IIIA (N1–N2)	EGFR mutant	483, gefitinib *vs.* vinorelbine + cisplatin (1:1)	100	2 years	DFS	HR, 0.6; P=0.0054
D'Angelo *et al.*, Retrospective (13)	I to III	EGFR mutant	1,118, erlotinib or gefitinib patients with resected IIIA (N2) disease also completed postoperative radiation therapy before starting adjuvant EGFR TKI	100	up to 2 years	Not reported	DFS HR, 0.43; P=0.001 OS HR, 0.50; P=0.076
Janjigian *et al.*, Retrospective (14)	I to III	EGFR mutant	167, gefitinib or erlotinib pre- and/or postoperatively, perioperative chemotherapy and radiation was allowed	100	up to 2 years	Not reported	2-year DFS; HR, 0.53 2-year OS; HR, 0.62
Kelly *et al.,* RADIANT phase III trial (15)	IB to IIIA (microscopic N2 only)	EGFR positive by IHC (≥1% staining) and\or FISH EGFR amplification	973, erlotinib *vs.* placebo (2:1) within 3 months from surgery or 6 months if they received chemotherapy	16.4	2 years	DFS	HR, 0.9; P=0.324
Neal *et al.*, SELECT phase II trial (16)	IA to IIIA	EGFR mutant	100, erlotinib after completion of any standard adjuvant chemotherapy and/or radiotherapy	100	2 years	DFS	2-year DFS, rate =90%
Goss *et al.*, BR19 phase III trial (17)	IB to IIIA	Without any EGFR selection	503, gefitinib *vs.* placebo within 26 weeks from surgery with or without previous adjuvant chemotherapy and/or radiotherapy	69	2 years	OS	HR, 1.24; P=0.14

NSCLC, non-small cell lung cancer; EGFR, epidermal grow factor receptor; DFS, disease free survival; HR, hazard ratio.

with adjuvant gefitinib compared to standard chemotherapy; data about OS are awaited to support the clinical use of gefitinib in adjuvant EGFR-mutated NSCLC.

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Footnote

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