Adjuvant EGFR TKIs in NSCLC harboring EGFR mutations: looking for a consensus way

Ilaria Attili[1,2], Antonio Passaro[1], Lorenzo Spaggiari[3,4], Gianluca Spitaleri[1], Filippo de Marinis[1]

[1]Division of Thoracic Oncology, IEO, European Institute of Oncology IRCCS, Milan, Italy; [2]Department of Surgery, Oncology and Gastroenterology, Faculty of Medicine, University of Padua, Padua, Italy; [3]Division of Thoracic Surgery, IEO, European Institute of Oncology, Milan, Italy; [4]Department of Oncology and Hemato-oncology, University of Milan, Milan, Italy

Correspondence to: Ilaria Attili, MD. Division of Thoracic Oncology, IEO, European Institute of Oncology IRCCS, Via G. Ripamonti, 435 - 20141 Milan, Italy. Email: ilaria.attili@ieo.it.

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Epidermal growth factor receptor (EGFR) sensitive mutations are routinely tested in advanced non-small cell lung cancer (NSCLC), with an incidence ranging from 10–15% in non-Asian to 30–50% in Asian patients (1). However, there is not a consensus on whether to test or not surgically resected NSCLCs for EGFR. Recently presented data show a positivity rate of 16% in completely resected NSCLC (2). In this journal Liang *et al.* reported a 2019 update of consensus on postoperative management of EGFR-mutant lung cancer of Society for Translational Medicine (3).

It is current standard of treatment for resected stage II-IIIA NSCLC patients, to receive adjuvant platinum-based chemotherapy (plus post-operative radiotherapy in pN2), when not received in neoadjuvant setting, with an overall 5% benefit in overall survival (OS) (4). The absolute overall 5-year survival ranged from 73% (IA) to 25% (IIIA), respectively, according to TNM staging (5). The survival advantage is obtained in all-comers NSCLCs, without considering the molecular profile of the resected tumors.

Following the usual clinical development shared by most anti-cancer drugs from advanced to early stage setting, EGFR tyrosine kinase inhibitors (EGFR TKIs) were rapidly moved to investigational adjuvant setting after the practice-changing results obtained in EGFR mutation positive aNSCLC (6-9). To date, six studies have complete results in this setting, with very heterogeneous inclusion criteria, treatment strategies and results (*Tables 1*,*2*). In particular, the negative phase III BR.19 (10) and RADIANT (11) trials were including patients unselected for EGFR status to receive EGFR TKI or placebo for 2 years after standard adjuvant treatment when needed. Three studies demonstrating prolonged disease free survival (DFS) with EGFR TKI treatment compared to standard chemotherapy—ADJUVANT (14), EVAN (15), EMERGING (17)—were limited to Chinese patients. In contrast, the non-randomized phase II SELECT trial, also showed positive results in DFS with 2-year erlotinib compared to placebo, following standard adjuvant treatment when needed according to disease stage (16).

Looking at data from these trials, all with unavailable or negative OS results, many questions arise on the effective role of adjuvant EGFR TKIs in clinical practice, and no clear consensus has been reached, so far. The first concern is about the position of the EGFR TKI within the adjuvant treatment strategy, whether given alone or with chemotherapy (in association or after). This latter strategy was investigated in the phase II P-C-G trial, demonstrating an increase in DFS with the addition of gefitinib to carboplatin pemetrexed in resected stage IIIA-N2 NSCLC (13). In contrast, a Chinese trial of combined icotinib and platinum based adjuvant treatment in resected stage IB-IIIA NSCLC, failed to show DFS advantage (12).

Another issue to define which could be the optimal

Table 1 Main studies on adjuvant EGFR TKIs in NSCLC

Study	Phase	Setting/stage	Treatment	Duration of EGFR TKI	Study result
BR19 (10)	3	IB-IIIA, resected[a]	Gefitinib *vs.* placebo*	2 years	Negative (OS)
RADIANT (11)	3	IB-IIIA, resected[a]	Erlotinib *vs.* placebo*	2 years	Negative (DFS)
CKC1102 (12)	2	IB-IIIA, resected	Icotinib plus platinum doublet	4–8 months	Negative (DFS)
P-C-G (13)	2	IIIA-N2, resected	Gefitinib plus carboplatin-pemetrexed	6 months	Positive (DFS)
ADJUVANT-CTONG 1104 (14)	3	II-IIIA, resected[b]	Gefitinib *vs.* cisplatin-vinorelbine	2 years	Positive (DFS)
EVAN (15)	2	IIIA, resected[b]	Gefitinib *vs.* cisplatin-vinorelbine	2 years	Positive (DFS)
SELECT (16)	2	IA-IIIA, resected	Erlotinib*	2 years	Positive (DFS)
EMERGING-CTONG 1103 (17)	2	IIIA-N2, neoadjuvant/adjuvant[a]	Erlotinib *vs.* cisplatin-gemcitabine	42 days to 1 year	Negative (ORR); positive (DFS)
ALCHEMIST-EGFR (2)	3	IB-IIIA, resected	Erlotinib *vs.* placebo*	2 years	Study ongoing
ADAURA (18)	3	IB-IIIA, resected	Osimertinib *vs.* placebo*	3 years	Study ongoing

[a], EGFR unselected; [b], only Chinese patients; *, previous standard adjuvant treatment allowed. EGFR, epidermal growth factor receptor; TKIs, tyrosine kinase inhibitors; NSCLC, non-small cell lung cancer; DFS, disease free survival; OS, overall survival; ORR, objective response rate.

Table 2 Results in the main studies on adjuvant EGFR TKIs in NSCLC

Study	Phase	Patients (n)	EGFR-TKI	DFS HR (95% CI)	Notes
BR19 (10)	3	503	Gefitinib ×2 yrs	1.22 (0.93 to 1.61)	Negative for 15 pts with EGFR+
RADIANT (11)	3	973	Erlotinib ×2 yrs	0.90 (0.74 to 1.10)	A positive trend for 161 EGFR+
CKC1102 (12)	2	41	Icotinib plus CT ×4–8 mos	NR	2-yr DFS 90.5%
P-C-G (13)	2	60	Gefitinib plus CT ×6 mos	0.37 (0.16 to 0.85)	Improved 2-yr DFS in IIIA
ADJUVANT-CTONG 1104 (14)	3	222	Gefitinib ×2 yrs	0.60 (0.42 to 0.87)	Improved 3-yr DFS
EVAN (15)	2	102	Gefitinib ×2 yrs	0.268 (0.13 to 0.53)	Improved 2-yr DFS in IIIA
SELECT (16)	2	100	Erlotinib ×2 yrs	NR	2-yr DFS 88% Retreatment data available

EGFR, epidermal growth factor receptor; TKIs, tyrosine kinase inhibitors; NSCLC, non-small cell lung cancer; DFS, disease free survival; HR, hazard ratio; CT, chemotherapy; NR, not reached.

duration of adjuvant EGFR-TKI treatment. In the past trials the duration of treatment ranged from 4 months to 2 years, but randomized clinical trials in other diseases (e.g., GIST and breast cancer) have demonstrated a clinical advantage on DFS with the extended regimen (3 or 5 or 10 years) (19,20).

Indeed, a role in neoadjuvant setting may be considered as well, according to stage, as it is for chemotherapy, and preliminary data from phase II trials are available in this setting (21). Another related aspect is the disease stage to consider for adjuvant EGFR: the EVAN trial and the P-C-G trial only included resected stage IIIA patients, representing a population usually undergoing neoadjuvant treatment, while other trials were including also stage I disease, not routinely candidate for adjuvant approaches according to international guidelines (22).

In addition, it is essential to keep in mind that the adjuvant setting concerns disease free patients, whose long-term quality of life (QoL) may be negatively affected by a long-term treatment with EGFR TKIs compared to the

time-limited adjuvant chemotherapy. The financial impact of such a long-term treatment, though the exact duration has not reached a consensus, should be also considered. The principal endpoint of all clinical trials in selected EGFR positive NSCLC patients was DFS, and the results of all these trials showed clearly that EGFR TKI can prolong DFS without improving the cure rates, so far all the aspects (optimal duration, which drug, safety profile and QoL) must be considered in this subset of patients. As far as it regards the choice of EGFR TKI for adjuvant treatment, it is important to note that the available data are related to first generation drugs erlotinib, gefitinib and icotinib. No specific information on TKI retreatment is known from the remaining studies save for SELECT trial. In the latter trial, patients received the same EGFR TKI at disease relapse, with a median on-treatment time of 13.1 months (16). These drugs are not corresponding to the current standard of treatment in first-line for EGFR mutant patients, that is the third generation TKI osimertinib. Complicating matters, the actual indication for osimertinib after previous EGFR TKI is conditional on the detection of T790M resistant mutation (23). To the current knowledge, limited information is available, deriving from the SELECT trial, were 60% of relapsing patients underwent rebiopsy, with confirmed EGFR mutation: T790M mutation was identified only in 5% (1 out of 20) of cases (16).

In conclusion, several phase II/randomized trials have been carried out in patients with EGFR positive resected NSCLC: they shared small sample size, included only common EGFR mutations and treatment duration was within 2 years. Overall, no clear indications can be derived from the available studies, where the OS results are negative or immature and only DFS advantage has been obtained (24). Interestingly, disease relapse mainly occurs after the completion of EGFR TKI, suggesting that the use of adjuvant EGFR TKIs may only anticipate the first-line treatment in EGFR mutant NSCLC patients. In this view, the final OS results from the randomized phase III ADAURA trial, evaluating the efficacy of 3-year third generation osimertinib compared to placebo in completely resected stage IB-IIIA EGFR mutant NSCLC patients, are awaited (18).

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Footnote

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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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