Adjuvant treatment of non-small cell lung cancer: focus on targeted therapy

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Abstract: In patients with completely resected stage II-IIIA non-small cell lung cancer (NSCLC), adjuvant platinum-based chemotherapy is associated with a modest, albeit significant, improvement in survival of approximately 5% at 5 years. However, regardless of whether adjuvant chemotherapy has been administered or not, the 5-year survival of these patients remains poor. In recent years, the discovery of targetable gene alterations such as epidermal growth factor receptor (*EGFR*) mutations and anaplastic lymphoma kinase (*ALK*) rearrangements has revolutionized the therapeutic approach to advanced NSCLC, owing to the introduction for clinical use of selective tyrosine kinase inhibitors (TKIs). The outstanding activity shown by EGFR- and ALK-TKIs in advanced NSCLC patients with *EGFR* mutations or *ALK* rearrangements, respectively, leads to the logical question of what role these agents may have if used in the adjuvant setting. In the present review we will discuss the emerging data that support the potential benefit of targeted therapy as adjuvant treatment of patients with completely resected NSCLC, and summarize the ongoing clinical trials which will eventually address this issue.

Keywords: Adjuvant treatment; anaplastic lymphoma kinase (*ALK*); epidermal growth factor receptor (*EGFR*); non-small cell lung cancer (NSCLC); targeted therapy; tyrosine kinase inhibitors (TKIs)

Introduction

Optimal management of selected patients with completely resected stage II-IIIA non-small cell lung cancer (NSCLC) include adjuvant cisplatin-based chemotherapy (1). In this patient population, the addition of adjuvant chemotherapy following surgery has resulted into an absolute improvement in survival of 4–5% at 5 years (2,3). A small survival benefit might also be observed for stage IB patients, though it appears to be mainly confined to high-risk patients, namely those with large tumors (T ≥4 cm) (4). Cisplatin-based doublets including vinorelbine, gemcitabine, docetaxel and pemetrexed (for non-squamous histology only) seem to be equally effective adjuvant treatments, while the addition

of bevacizumab, an anti-VEGF monoclonal antibody, to platinum-based chemotherapy was not found to improve survival in a randomized phase 3 trial (5).

In the era of precision medicine, predictive biomarkers have revolutionized the therapeutic approach to advanced disease. The best described targetable alterations are sensitizing epidermal growth factor receptor (*EGFR*) mutations in exon 19 (ex19del) and exon 21 (L858R), which account for roughly 90% of all EGFR-mutated NSCLCs, and echinoderm microtubule-associated protein-like 4 (*EML-4*)-anaplastic lymphoma kinase (*ALK*) rearrangements (6,7). Taken together, *EGFR* mutations and *ALK* rearrangements can be detected in up to 20% of

advanced NSCLCs, and are preferentially found in non-squamous histology and/or young patients with never/light smoking history. Importantly, selective tyrosine kinase inhibitors (TKIs) have been developed for the treatment of NSCLCs that harbor these targetable gene alterations, namely gefitinib, erlotinib, and afatinib that target the tyrosine kinase domain of EGFR, and crizotinib that inhibits the tyrosine kinase domain of ALK fusion protein. In clinical trials, EGFR- and ALK-TKIs have been shown to improve progression-free survival (PFS) and response rates over platinum-based chemotherapy in biologically selected patients with EGFR-mutated and ALK-positive advanced NSCLC, respectively, thus emerging as a standard first-line option in this setting (6,8,9).

On this basis, it is reasonable to consider the use of targeted therapy also as adjuvant treatment of patients with resected tumors that harbor *EGFR* mutations or *ALK* rearrangements. The present review will briefly discuss the present and future of targeted therapy for patients with completely resected NSCLC.

Rationale for adjuvant targeted therapy

At the present time there is no evidence suggesting a worse prognosis for EGFR-mutated NSCLC in early stage disease. A recent meta-analysis of 14 studies involving 2,652 cases of completely resected NSCLCs (EGFR-mutated =1,033, 39%) found that disease-free survival (DFS) of EGFR-mutated patients was not significantly different from that of EGFR wild type patients (HR 0.87; 95% CI 0.65–1.16) (10). Although this study did not address the impact of adjuvant chemotherapy in the analyzed population, it still provides compelling results on the fact that *EGFR* mutation is not prognostic in completely resected NSCLC. Similarly, retrospective studies exploring the impact of *ALK* rearrangements in early stage NSCLC suggested that ALK status lacks a prognostic role, as no significant difference in DFS was found between ALK-rearranged and ALK-negative patients (11,12). Nevertheless, *EGFR* mutations and *ALK* rearrangements are both highly predictive of response to selected targeted therapy in advanced NSCLC.

Against this background, a number of retrospective studies have suggested that targeted therapy has a role as adjuvant treatment of completely resected NSCLCs with EGFR-mutated NSCLC. The first study to set the stage for adjuvant EGFR-TKIs was published from Janjigian and colleagues who reported their experience on 167 patients with EGFR-mutated (ex19del and L858R) completely

resected stage I-III NSCLC (13). Peri-operative (either adjuvant or neoadjuvant) gefitinib or erlotinib were administered in 56 patients (33%), the majority of whom (n=30, 54%) had stage I disease. In a multivariate analysis adjusted for sex, pathologic stage, type of surgery, and adjuvant cisplatin-based chemotherapy, patients treated peri-operatively with an EGFR-TKI had a 2-year DFS rate of 89% compared with 72% for patients who did not receive an EGFR-TKI (HR 0.53; 95% CI: 0.28–1.03; P=0.06). The 2-year overall survival (OS) was 96% versus 90%, respectively (HR 0.62; 95% CI: 0.26–1.51; P=0.296). Interestingly, an update analysis of 286 patients of whom 84 (29%) were treated with peri-operative gefitinib or erlotinib showed a significantly longer DFS in favor of adjuvant EGFR-TKI (HR 0.43; 95% CI: 0.26–0.72; P=0.001), with a non-significant trend for improved OS (HR 0.50; 95% CI: 0.23–1.08; P=0.076) (14). More recently, Lv and colleagues evaluated retrospectively 257 patients with completely resected stage I–IIIA NSCLC, of which 138 (53.7%) tested positive for an *EGFR* mutation (ex19del and L858R in 132 patients, 51.4%) (15). Among the EGFR-mutated population with ex19del and L858R they compared the patients who received an adjuvant EGFR-TKI (n=30) versus those who did not (n=102), and found a significantly higher DFS in the EGFR-TKI-treated group (P=0.033). Adjuvant EGFR-TKIs were not associated with improved OS (P=0.258), although the recipients had better 3-year OS (92.5% *vs.* 81%). However, approximately half of the patients treated with an adjuvant EGFR-TKI had stage IIIA disease, meaning that the benefit in DFS could have been largely driven by this high risk population. At the present time, no retrospective studies on the potential impact of an ALK-TKI on the outcome of ALK-positive early stage NSCLC have been reported.

Prospective trials of adjuvant targeted therapy

As shown in *Table 1*, a few prospective trials have investigated an EGFR-TKI as adjuvant treatment for patients with completely resected NSCLC. Unfortunately, most of these trials present with caveats in the study design and conduction. Among these, NCIC CTG BR.19, in which patients with completely resected stage IB-IIIA NSCLC treated or not with adjuvant platinum-based chemotherapy were randomized to either gefitinib or placebo for 2 years (16). Unfortunately, this trial was prematurely closed after randomizing only 503 of the 1,242 patients that were initially planned. This was the consequence of the negative

Table 1 Prospective trials of an EGFR-TKI as adjuvant treatment

Author, phase	Stage, biomarker selection	No. of pts, design	Length of exposure to EGFR-TKI	Primary end-point	Results for primary end-point
Goss *et al.*, 3 (NCIC CTG BR.19) (16)	IB–IIIA, unselected	503, gefitinib *vs.* placebo	2 years	OS	HR =1.24, P=0.14
Kelly *et al.*, 3 (RADIANT) (17)	IB→IIIA, EGFR + by IHC and/or FISH	973, erlotinib *vs.* placebo (2:1)	2 years	DFS	HR =0.90, P=0.324
Pennel *et al.*, 2 (SELECT) (18)	IA→IIIA	100, erlotinib	2 years	DFS	2-year DFS rate =90%
Li *et al.*, 2, randomized (19)	IIIA (N2), EGFR mutation[≠]	60, CBDCA/PEM → gefitinib *vs.* carboplatin/pemetrexed	6 months	DFS	HR =0.37, P=0.014
Feng *et al.*, 2, randomized (20)	IB (high risk)*→IIIA, EGFR mutation[∞]	41, platinum-based chemotherapy → icotinib *vs.* platinum-based chemotherapy	4–8 months	DFS	2-year DFS 90.5% *vs.* 66.7%, P=0.066
Wu *et al.*, 3 (CTONG 1104) (21)	II–IIIA (N1,N2)**, EGFR mutation[≠]	222, gefitinib ×2 years *vs.* cisplatin/vinorelbine	2 years	DFS	28.7 *vs.* 18.0 months, HR =0.60, P=0.05

Adjuvant chemotherapy allowed (NCIC CTG BR.19; RADIANT; SELECT); adjuvant radiotherapy allowed (NCIC CTG BR.19; SELECT). *, poorly differentiated tumors, vascular invasion, wedge resection, tumor size >4 cm, visceral pleural involvement, incomplete lymph node sampling; **, 7th TNM staging; [≠], exon 19 deletion or exon 21 L858R; [∞], exon 19 deletion, exon 21 L858R, exon 18 G719X, econ 21 L861Q. DFS, disease-free survival; EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor; HR, hazard ratio; No., number; OS, overall survival; pts, patients; *vs.*, versus.

outcomes observed in other phase 3 studies evaluating the role of gefitinib in either locally advanced disease or second-line setting (22,23). Therefore, the results of this study are totally uninformative. More recently, the results of the RADIANT trial, a phase 3 randomized, placebo-controlled trial of adjuvant erlotinib versus placebo for patients with stages IB–IIIA were published (17). In this study, 973 patients selected based on EGFR positivity by immunohistochemistry and/or fluorescence *in situ* hybridization were randomized in a 2:1 ratio to either erlotinib or placebo for 2 years, the primary end-point being DFS. Fifty-one percent of patients had stage IB disease, and approximately 52.9% of enrolled patients received adjuvant chemotherapy. The trial reported that DFS was not significantly different between the two arms of treatment [median 50.5 months for erlotinib and 48.2 months for placebo (HR =0.90; 95 % CI: 0.74–1.10; P=0.324)], while OS data were immature at a median follow-up of 47 months. Interestingly, a trend in favor of erlotinib was evident in the subgroup of patients with an *EGFR* mutation (ex19del and L858R) (n=161, 16.5%) [median 46.4 months for erlotinib and 28.5 months for placebo (HR =0.61; 95 % CI: 0.38–0.98)]. However, this finding should be interpreted with caution owing to the fact that the *EGFR* mutant

patients assigned to the placebo arm underperformed when compared to the overall placebo-treated population, likely reflecting an imbalance in terms of patients characteristics (significantly more stage IIIA patients in the *EGFR*-mutated group treated with placebo) (17). More recent trials had the advantage to focus exclusively on the population of patients with an *EGFR* mutation, with promising results in terms of clinical outcome (18-20). Unfortunately, they were either uncontrolled studies (18) or randomized phase II studies (19,20) not powered enough in order to lead to conclusive results that could change clinical practice. Nevertheless, their results were consistent in suggesting that when patients are selected based on the presence of an *EGFR* mutation, adjuvant treatment with an EGFR-TKI with or without prior adjuvant chemotherapy is associated with a 2-year DFS ranging from 90% to 92.4%. Of note, these results are in line with the 2-year DFS of 89% reported by Janjigian and colleagues in their retrospective study (13). On this basis, a meta-analysis was conducted in order to evaluate the role of an adjuvant EGFR-TKI for EGFR-mutated completely resected NSCLCs (24). The results suggested a 9.5% absolute improvement in DFS at 3 years for EGFR-mutated NSCLCs treated with an adjuvant EGFR-TKI (HR =0.48), with a marginal, albeit statistically

Table 2 Ongoing randomized phase 3 trials of an EGFR-TKI as adjuvant treatment for patients with EGFR mutant NSCLC

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, 477, 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. Rand., randomization; vs., versus; DFS, disease-free survival; OS, overall survival.

significant, benefit also in OS (HR =0.72). Although intriguing, the results of this meta-analysis are flawed by the fact that two of the five included studies were retrospective analyses, in which the patients who received an EGFR-TKI were not randomized to that therapy, thus potentially biasing the overall results (14,15).

Recently, at ASCO 2017, Wu and colleagues reported the data coming from a randomized trial comparing gefitinib for 2 years versus four cycles of standard chemotherapy (cisplatin 75 mg/m^2 day 1 + vinorelbine 25 mg/m^2 days 1 and 8, every 3 weeks) in patients with completely resected stage II–IIIA NSCLC harboring an *EGFR* mutation (ex19del and L858R) (21). The primary end-point of the study, which was to demonstrate a 40% (HR =0.60) or greater improvement in DFS in favor of the gefitinib arm, was met. Two-hundred and twenty-two patients were randomized (111 in each arm), and median DFS was 28.7 months for gefitinib versus 18.0 months for chemotherapy (HR 0.60; 95% CI: 0.42–0.87; P=0.005), which translates into a 10.7 months improvement between the two treatments. Some points need to be addressed with regard to this study. First, it was conducted exclusively in a Chinese population. Secondly, it mainly focused on patients at high risk of

recurrence, as documented by the fact that only individuals with pathologic lymph-node involvement N1-N2 were included. With this in mind, this study suggests that, when patients are properly selected based on the presence of an *EGFR* mutation, the benefit in favor of targeted therapy is clinically significant, and an EGFR-TKI may even replace adjuvant chemotherapy in this context. However, ongoing confirmatory studies will be crucial in order to assess the impact of an adjuvant EGFR-TKI in completely resected NSCLCs with an *EGFR* mutation.

Ongoing studies

Table 2 shows ongoing phase 3 randomized trials of targeted therapy as adjuvant treatment of completely resected NSCLC. In all of them, patients are selected for the appropriate targeted therapy based on the presence of either an *EGFR* mutation or *ALK* rearrangement. Importantly, these studies will provide an answer to most of the pending issues. First of all, should an EGFR-TKI be used sequentially after platinum-based chemotherapy (NCT02125240, NCT01996098, and NCT02193282/ NCT02201992)? Rather, similarly to what has been

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suggested by Wu and colleagues, can an EGFR-TKI replace adjuvant chemotherapy as stand-alone treatment (WJOG6401L and NCT024488797)? Furthermore, what is the role for an EGFR-TKI given concomitantly with adjuvant chemotherapy (NCT02518802)? Finally, what is the optimal duration of adjuvant EGFR-TKI (NCT01996098)? With regard to the last issue, virtually all ongoing trials, in the absence of recurrence and/or unacceptable toxicity, anticipate that treatment with an EGFR-TKI should be continued for 2 years. However, such duration is to be balanced against the potential harm of treatment. In the RADIANT trial, in which erlotinib was also designed to be given for 24 months, the median duration of treatment was only 12 months for erlotinib versus 22 months for placebo, suggesting intolerance. In addition, as expected, the incidence of any grade adverse events was significantly higher with erlotinib versus placebo, the most common grade ≥3 adverse events being rash (22.3% *vs.* 0.3%) and diarrhea (6.2% *vs.* 0.3%) (17). On the other hand, a shorter duration of treatment may be still beneficial with the potential advantage of antagonizing the onset of biological resistance to treatment. According to this hypothesis, it has been demonstrated that patients who develop recurrence after stopping adjuvant EGFR-TKI are usually sensitive to re-treatment, while those who recur while on adjuvant EGFR-TKI are more likely to bear the exon 20 T790M mutation, which is associated with resistance to either first or second-generation EGFR-TKIs (gefitinib, erlotinib or afatinib) (25). With regard to this, the third-generation EGFR-TKI osimertinib has been demonstrated superior to gefitinib or erlotinib in first-line *EGFR*-mutated advanced NSCLCs (26). Similarly, the use of adjuvant osimertinib might prove beneficial, and the International study "ADAURA" is ongoing in order to compare osimertinib versus observation after standard adjuvant chemotherapy (NCT02511106).

Conclusions and future directions

The aim of adjuvant treatment is to eradicate minimal residual disease. One of the concerns with adjuvant targeted therapy for completely resected NSCLCs is that it can only suppress rather than eliminate the growth of residual disease. If this is the case, patients who do not receive adjuvant targeted therapy may derive equal benefit by receiving it at recurrence. For this reason, the use of adjuvant targeted therapy could be justified only in presence of an OS benefit.

Another critical issue is how to select the patients who may need adjuvant targeted therapy. Measurement of residual disease by circulating tumor cells and/or DNA could help identify the high-risk population. However, for these patients it should be clarified whether targeted therapy should be used sequentially after platinum-based chemotherapy or as stand-alone treatment; in addition doubts may exist on the optimal duration of targeted therapy in patients for whom residual disease after surgery is documented.

Finally, as we move towards a better understanding of the mechanisms that underlie resistance to targeted therapy in advanced NSCLC, clinical research should rapidly apply the new knowledge to clinical trials of adjuvant treatment. Therefore, better understanding of the biology at recurrence and novel testing strategies for residual disease are crucial in order to help select those patients who could benefit the most from adjuvant targeted therapy.

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