Targeted therapies for unresectable stage III non-small cell lung cancer

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Abstract: Until recently, the standard treatment in unresectable stage III non-small cell lung cancer was concurrent chemoradiotherapy, but often with dismal outcome. The introduction of consolidation treatment with immune checkpoint inhibitors has shifted the treatment landscape and prognosis of these patients. However, patients whose tumors harbors an epidermal growth factor receptor (EGFR) mutation derived less benefit, with an increased risk of immune-related adverse events. Moreover, current data suggested that patients with oncogenic addicted tumors, mainly EGFR-positive tumors, and also anaplastic lymphoma kinase (ALK)-positive have poorer progression free survival after chemoradiotherapy. Indeed, these tumors have also inferior distant control compared with those who have wild-type disease, especially in the central nervous system, highlighting the need for assessing the role of targeted therapies in this patient population. It is speculated that outcome could probably increase with a consolidation treatment strategy including an EGFR tyrosine kinase inhibitor. However, a personalized treatment approach is not considered standard of care in this setting due to lack of robust evidence, as the majority of trials were performed in unselected patients, number of patients is limited and the majority of these studies were underpowered. In this review we summarize the role of tyrosine kinase inhibitors in unresectable stage III NSCLC, specifically focusing on EGFR-mutant tumors.

Keywords: EGFR-mutant; chemo-radiotherapy; non-small cell lung cancer (NSCLC); sequential; concurrent

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Introduction

Non-small cell lung cancer (NSCLC) represents 85% of all primary lung cancers, and approximately 20% to 25% of these patients present with locally advanced disease (stage III) (1). Of note, the proportion of new lung cancer cases presenting as stage III has decreased steadily, from 28.6% in 1998 to 26.6% in 2006, possibly as a consequence of an increase in stage IV NSCLC after the year 2000 (from 35.7% to 39.4%). This data probably reflects the widespread adoption of fluor-deoxyglucose positron emission tomography (FDG-PET) scans and magnetic resonance imaging (MRI) of the brain leading to a better radiological assessment and staging (2). Concurrent chemoradiotherapy (cCT-RT) remains the standard treatment approach for...
patients with unresectable stage III NSCLC and good performance status (1). However, before 2017 the prognosis for these patients was still dismal, with a median overall survival (OS) ranging from 19.6 months to 28.7 months (3-5), and a 5-year OS rate ranging from 15% to 32.1% in more recent series (1,5). Different strategies have been tested with the aim to improve the outcome in this population. Radiation dose escalation and the addition of cetuximab to cCT-RT treatment did not provide any survival benefit compared with the standard approach while increasing treatment-related toxicities (5). Likewise, maintenance treatment with vaccination after chemo-radiotherapy did not improve the survival in the whole population compared with placebo (6). Finally, the addition of bevacizumab was not recommended given the lack of an efficacy signal and the substantial risk of esophageal toxicity (7).

After 2017, the phase III PACIFIC trial shifted the treatment paradigm in unresectable stage III NSCLC patients. The trial reported that consolidation treatment with one year of durvalumab after cCT-RT compared with placebo significantly improved the progression free survival (PFS: 17.2 vs. 5.6 months, Hazard Ratio, HR =0.51, 95% CI: 0.41–0.63, P<0.0001) (8) and the OS (47.5 vs. 29.1 months, HR 0.71, 95% CI: 0.57–0.88) with a 4-year OS of 49.6% vs. 36.3%, respectively (9). The benefit of durvalumab occurred without detrimental effect on patient-reported outcomes (10). Programmed cell death-ligand 1 (PD-L1) status was not mandatory for inclusion in the PACIFIC trial, and PD-L1 status was unknown in 37% of all randomized patients. A prespecified exploratory analysis assessed the benefit of durvalumab according to PD-L1 expression ≥25% or <25% (by SP263 IHC assay) and confirmed the benefit regardless of PD-L1 expression level. However, a post-hoc analysis requested by the European Medicines Agency (EMA) with a PD-L1 expression-level cut-off of 1% suggested that PFS benefit with durvalumab occurred across all subgroups, but an OS benefit was found only in those tumors with a PD-L1 ≥1% tumors (9,11). Based on these data, the FDA approved consolidation durvalumab as a new standard of care regardless of PD-L1 expression in February 2018, whereas the EMA approval in September 2018 was limited to the PD-L1 ≥1% tumors. Likewise, the recent phase II LUN 14-179 clinical trial (12) has reported that consolidation pembrolizumab after cCT-RT did also improve the outcome in comparison with historical controls, endorsing the immune-strategy in this setting. Finally, preliminary data of trials evaluating immunotherapy concurrent with cCT-RT are also promising (13,14).

This new standard therapeutic approach put into question whether all patients with locally advanced NSCLC may obtain benefit of an immunotherapy consolidation strategy after cCT-RT. This is especially relevant for oncogenic addicted tumors. In the metastatic setting, this subpopulation of lung tumors did obtain only a limited efficacy with immune checkpoint inhibitors as monotherapy (15), and in locally advanced disease, the PACIFIC trial did not improve the outcome with durvalumab compared with placebo among the 6% of epidermal growth factor receptor (EGFR)-mutant tumors enrolled in the trial (9). Indeed, in real world data, consolidation with durvalumab appears to be less efficacious in patients with ERBB2/EGFR mutant tumors (tumors harboring ERBB2/EGFR mutation had a significantly shorter disease free survival compared to the EGFR/ERBB2 wildtype tumors, 7.5 months vs. not reached, P=0.04) (16). Of note, a retrospective analysis of 37 patients with unresectable stage III EGFR-mutated NSCLC assessed the role of consolidation strategy either with durvalumab or EGFR tyrosine kinase inhibitor (TKI) after completion of cCT-RT. Out of these 37 patients, 13 initiated durvalumab a median of 20 days after cCT-RT completion. Two patients completed 12 months of treatment, with five patients discontinuing durvalumab due to progression and five due to immune-related adverse events (irAEs). Of 24 patients who completed cCT-RT without durvalumab 16 completed CRT alone and 8 completed cCT-RT with induction or consolidation EGFR TKI. Median PFS was 10.3 months in patients who received cCT-RT and durvalumab versus 6.9 months with cCT-RT alone (log-rank P=0.993). The cCT-RT and EGFR TKI was associated with a significantly longer median PFS (26.1 months) compared to cCT-RT and durvalumab or CRT alone (log-rank P=0.023) (17). Similarly, the REFRACT study, a pooled retrospective analyses including patients with locally advanced NSCLC and EGFR mutation, reported that radiotherapy plus EGFR TKI with or without chemotherapy was associated with improved PFS relative to chemo-radiotherapy (HR =0.42, 95% CI: 0.29–0.61, P<0.001) and OS (HR =0.60, 95% CI: 0.37–0.99, P=0.045), as well as improved PFS compared to EGFR TKI as monotherapy (HR =0.65, 95% CI: 0.47–0.90, P=0.008) and marginally better OS relative to TKI (HR =0.67, 95% CI: 0.41–1.11, P=0.12). The improved outcome with the addition of EGFR TKI to standard chemo-radiotherapy could be related to better local and distant control. These data may suggest the increased risk of toxicity among...
EGFR-mutant tumors with consolidation treatment with durvalumab and the potential role of exploring personalized approaches with TKI against oncogenic drivers in this setting, being an area of ongoing and for future research.

**Personalized treatment in locally-advanced disease**

The discovery of targetable oncogenic drivers in advanced NSCLC (18) and the development of targeted therapies against these targets, mainly TKI and antibody drug conjugated drugs, have revolutionized the therapeutic strategy in this setting (19,20). This strategy provides a personalised treatment approach in advanced NSCLC contributing to an improvement in the OS (21), as well as a reduction in lung cancer mortality in most recent years (22).

Of note, genomic alterations reported in advanced tumours are also found in early stage lung cancers (18), challenging the role of personalised treatment in unresectable stage III NSCLC.

**EGFR mutation**

In the metastatic setting, the prevalence of EGFR mutations is around 10–20% in the Caucasian population with adenocarcinoma but much higher in Asian populations (~50%). Around 90% of the most common EGFR mutations comprise deletions in exon 19 and the L858R substitution mutation in exon 21. These mutations confer sensitivity to EGFR TKI (19,20). In EGFR-mutant advanced NSCLC, first-generation (gefitinib and erlotinib) and second-generation EGFR TKI (afatinib and dacomitinib) resulted in an improved outcome compared with the standard of care (19,20). Recently, the phase III FLAURA trial reported that osimertinib, a third-generation EGFR TKI, improved the PFS and OS compared with first-generation EGFR TKI with better intracranial activity. As a result, osimertinib became the preferred upfront strategy in this subset of lung adenocarcinomas (23). Likewise, osimertinib has once again shifted the treatment paradigm with the phase III ADAURA results, this time in completely resected stage I-IIIA NSCLC with common EGFR mutations reporting a significant improvement in disease free survival compared with placebo after optional adjuvant chemotherapy (24).

Some studies have reported that EGFR mutation prevalence in locally advanced NSCLC ranges from 10% to 30% (25–27), probably as a consequence of the different ethnicity population tested. The outcome of chemo-radiotherapy in unresectable stage III disease harboring oncogenic drivers remains controversial. Some authors (26,28) have reported that median PFS after radical chemo-radiotherapy was significantly shorter in stage III EGFR-mutant compared with wild-type tumors (9.6 vs. 12.0 months; multivariate HR 2.0, 95% CI: 0.9–4.2, P=0.003), although no differences in OS were reported (29.4 vs. 23.4 months, P=0.21) (26). In contrast, other authors have reported longer median OS in EGFR-mutant tumors compared with wild-type tumors, although the difference was not statistically significant (29,30). Meanwhile, the frequency of distant metastases in EGFR-mutant tumors after cCT-RT was higher than in the wild type tumors or tumors with other oncogenic alterations (28,29,31). This was especially found for brain metastases with a cumulative incidence of brain metastases at 3-years and 5 years of 33% and 44%, respectively (31). These data along with data from a systematic review and meta-analysis suggest that stage III EGFR-mutant tumors have shorter PFS on cCT-RT than wild type, mainly because of distant metastasis relapse, especially brain metastases, regardless of better local control (32). Based on the efficacy of EGFR TKI in the metastatic setting and in early-stage EGFR-mutant NSCLC, especially with osimertinib, the EGFR TKI strategy was started to be tested in unresectable stage III EGFR-mutant NSCLC with the aim of extending the positive results in this setting and change the natural history of this disease.

A retrospective study assessed whether EGFR TKI (n=177) could substitute the cCT-RT (n=22) in stage III EGFR-mutant NSCLC patients. The study did not find differences in OS (HR 0.71, 95% CI: 0.34–1.47) or lung cancer-specific survival (HR 0.65, 95% CI: 0.31–1.35), yielding a 5-year OS of 30% and 25%, respectively (33). The limited number of patients and the retrospective nature of this analysis do not lead to obtain firm conclusions whether EGFR TKI alone may be the preferred treatment option instead of the cCT-RT in EGFR-mutant unresectable stage III NSCLC.

Preclinical studies have suggested that EGFR-mutant NSCLC cells have a predominantly radiosensitive phenotype and EGFR TKI may have a radiosensitizing effect (34,35). These data provide rationale to assess the application of EGFR TKI either in combination with radiotherapy or as a consolidation or maintenance strategy after cCT-RT (Table 1). However, it is relevant to mention that a recent modeling study predicted that targeted induction therapies before chemo-radiotherapy may render adjuvant targeted therapy less effective due to proliferation.


Table 1 Clinical trials with EGFR TKI in locally advanced disease

| Strategy                          | References       | EGFR mutant |
|----------------------------------|------------------|-------------|
| EGFR TKI vs. cCT-RT              | (33)             | Yes         |
| EGFR TKI + RT vs. sCT-RT         | (36)             | Yes         |
| EGFR TKI + cCT-RT/sCT-RT         | (37-39)          | No          |
| EGFR TKI + RT                    | (40)             | No          |
| EGFR TKI → EGFR TKI + cCT-RT     | (41)             | Yes         |
| EGFR TKI → cCT-RT                | (42)             | Yes         |
| cCT-RT → EGFR TKI                | (43)             | No          |
|                                   | (44)             | Yes         |

NCT04636593, RTOG 1306 (NCT01822496), NCT03396185

cCT-RT, concurrent chemotherapy-radiotherapy; sCT-RT, sequential chemotherapy-radiotherapy.

of drug-resistant cancer cells when using very long induction periods (45).

The randomized phase II RECEL (NCT0174908) screened 252 patients and enrolled 41 unresectable EGFR-mutant stage III NSCLC patients, who were randomized to erlotinib for 2 years plus radiotherapy or cCT-RT. In the erlotinib arm the PFS significantly improved compared with the cCT-RT arm (27.9 vs. 6.4 months, HR 0.053, 95% CI: 0.006–0.463, P<0.001), with the same incidence of adverse events (AEs, grade ≥1, 86.7%, 13/15) being the most common AEs grade ≥3 the rash (20%) and hematological toxicity (27%) (36). This data provides rationale for the role of EGFR TKI before cCT-RT in EGFR-mutant tumors, but warrants further evaluation in a phase III clinical trial. A similar strategy is being explored in the ongoing single arm phase II WJOG6911L study with gefitinib (46).

The addition of EGFR TKI to a chemo-radiotherapy strategy has been assessed in phase II trials, but most of these trials included patients either with wild-type or unknown EGFR status. The CALGB 30106 trial assessed the addition of gefitinib to sequential or cCT-RT in 63 unresectable stage III NSCLC patients. In this trial all patients received 2 cycles of induction chemotherapy plus gefitinib followed by radiotherapy plus gefitinib in poor performance status patients, or cCT-RT plus gefitinib in good-risk patients. Although the toxicity was not increased, compared with historical data, the median OS data was very disappointing (19 and 13 months in the poor-risk and good-risk group, respectively). There were no differences in PFS (P=0.87) or OS (P=0.88) among 13 EGFR-mutant tumors compared with wild-type tumors (37). Similar outcomes were reported in another phase II trial (CALGB30605) (40) assessing erlotinib plus radiotherapy after 2 cycles of induction chemotherapy in poor-risk stage III NSCLC patients (PFS: 11 months, OS: 17 months). However, no patients with EGFR mutation were identified in this trial. In contrast, two phase II trials reported promising survival data either with gefitinib and concurrent thoracic radiotherapy after induction chemotherapy (38) or erlotinib plus cCT-RT (39), reaching a 2-year OS rate of ~65%. These findings may suggest a survival benefit with EGFR TKI in this setting, although EGFR mutation was not mandatory and only 5 EGFR-mutant patients were included in the former study (39), limiting the potential conclusions in this subset of lung adenocarcinomas. Among 12 EGFR-mutant unresectable stage III NSCLC patients, induction treatment with erlotinib followed by either cCT-RT plus erlotinib (N=7) or by cCT-RT (N=5) did not report differences either in OS (39.3 vs. 31.2 months, P=0.442) or in PFS (11.6 vs. 8.1 months, P=0.134). Although EGFR-mutant tumors had better OS than wild-type EGFR tumors (74.8 vs. 25.3 months, P=0.034) probably related to subsequent EGFR TKI therapies at the time of progression, the distant failure rate was higher in EGFR-mutant tumors compared with wild-type tumors (63% vs. 42%, P=0.463). This was especially found for brain metastases, as these were the more common site of the first relapse in the EGFR-mutant group, even though there was no statistical significant difference between groups (46% vs. 18%, P=0.070) (41). This data may suggest that EGFR TKIs with higher intracranial penetration is necessary in this setting if we want to change the natural history of this disease.

Finally, two phase 2 clinical trials assess the role of induction EGFR TKI before cCT-RT in EGFR mutant stage III tumors, the LOGIK0902/OLCSG0905 intergroups study with gefitinib (42), and the RTOG 3106 (NCT01822496) with induction erlotinib followed by cCT-RT or only CT-RT. The later trial has terminated due to lack of accrual.

Maintenance strategy with EGFR TKI in an unselected population was assessed in the phase III SWOG S0023 trial (43). Patients who did not progress after cCT-RT with platinum and etoposide and three cycles of consolidation with docetaxel were randomized to maintenance treatment with gefitinib or placebo for 5 years. The study was closed.
prematurely as after a median follow-up of 27 months, median OS was 23 months with gefitinib, whereas it reached 35 months with placebo (P=0.013). The decreased survival was primarily due to disease progression rather than treatment toxicity, as toxic death rate was not different from placebo (2% vs. 0%). It is important to notice that this trial did not select patients according to \textit{EGFR} mutation status. Perhaps selectively treating patients only with \textit{EGFR} mutations with gefitinib may lead to different outcomes.

Despite limited data about \textit{EGFR} TKI efficacy for patients with stage III \textit{EGFR}-mutant NSCLC, evidence has suggested that these patients have inferior distant control following platinum-based CRT compared with those who have \textit{EGFR} wild-type disease, especially central nervous system (CNS) control (32), highlighting the need for targeted therapy in patients with these disease features. The phase 3 LAURA clinical trial (NCT03521154) is currently enrolling unresectable \textit{EGFR}-mutant stage III NSCLC patients to explore the efficacy and safety of osimertinib compared with placebo (2:1) until progression as maintenance therapy in patients without progression after concurrent or sequential chemoradiation (44). The primary end point is PFS per RECIST 1.1 according to blinded independent central review (BICR); and secondary end points include CNS PFS, PFS by mutational status, OS, safety, and tolerability (Figure 1). Moreover, almonertinib, a new third generation \textit{EGFR} TKI is being tested in a phase II trial combined with thoracic radiotherapy in stage III NSCLC with an activating \textit{EGFR} mutation (NCT04636593). Similarly, the first-generation \textit{EGFR} TKI icotinib is being tested in a single arm phase II trial as maintenance therapy after sequential or cCT-RT in the same patient population (NCT03396185). Primary endpoint is OS. Furthermore, a retrospective Chinese cohort of stage III and \textit{EGFR}-mutant NSCLC patients is assessing the best treatment approach in this setting: chemoradiotherapy, chemoradiotherapy plus \textit{EGFR} TKI, or \textit{EGFR} TKI alone (NCT04304638). The results of this trial may help to state the role of \textit{EGFR} TKI in locally advanced setting.

\textit{ALK} rearrangement

In locally advanced disease, the prevalence of \textit{ALK} rearrangement ranges from 2\% to 8\% (25,26,46). Poorer PFS has been reported in \textit{ALK}-positive tumors after chemoradiotherapy compared with wild type (6 vs. 12 months, HR 2.8, 95\% CI: 1.5–5, P=0.003). Based on the efficacy of \textit{ALK} TKI in the metastatic setting (47,48) it is logic to explore the role of these drugs in the locally advanced setting. For now, only the RTOG 3106 (NCT01822496) has randomized stage III \textit{ALK}-positive NSCLC patients to receive either induction with crizotinib for three months followed by cCT-RT or only cCT-RT. This trial has terminated due to the poor accrual.

\section*{Conclusions}

The current evidence does not support the use of TKI in oncogenic addicted tumors in stage III. However, the limited efficacy of chemo-radiotherapy for these tumors
(EGFR/ALK) and risk of distant metastases support to further explore the use of TKI in this setting. Another challenge today is whether oncogenic addicted tumors should or should not receive consolidation immunotherapy after cCT-RT based on limited efficacy, as well as the finding that sequential immunotherapy followed by a TKI may increase toxicity. Therefore, the optimal strategy in stage III NSCLC patients with oncogenic drivers deserves further evaluation.

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