Targeted Therapy and Immunotherapy in Early-Stage NSCLC

Subjects: Oncology

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The scenario of neoadjuvant and adjuvant settings in non-small cell lung cancer (NSCLC) is rapidly evolving. As already happened for the advanced disease, also early stages have entered the era of precision medicine, with molecular analysis and Programmed death-ligand 1 (PD-L1) evaluation that by now can be considered a routine assessment. New treatment options have been approved, with osimertinib now part of clinical practice for Epidermal Growth Factor Receptor mutated (EGFRm) patients, and immune checkpoint inhibitors (ICIs) available after FDA approval both in the adjuvant (atezolizumab) and neoadjuvant (nivolumab) setting. Several clinical trials with specific-tyrosine kinase inhibitors (TKIs) and ICIs are ongoing, both with and without concomitant chemotherapy. As therapeutic strategies are rapidly expanding, quite a few questions remain unsettled, such as the optimal duration of adjuvant targeted therapy or the effective benefit of ICIs in early-stage EGFRm or ALK (Anaplastic Lymphoma Kinase) rearranged patients, or the possibility to individuate high-risk patients after surgical resection assessing minimal residual disease (MRD) by ctDNA evaluation.

Keywords: non-small cell lung cancer ; early stage ; adjuvant therapy ; neoadjuvant therapy ; targeted therapy ; tyrosine kinase inhibitors ; EGFR mutations ; ALK rearrangements ; immunotherapy ; immune checkpoint inhibitors

1. Introduction

A platinum-based two-drug combination chemotherapy (CT) represents the standard adjuvant treatment in resected non-small cell lung cancer (NSCLC) with a pathologic stage II or III according to the American Joint Committee on Cancer (AJCC) tumor-nodes-metastases (TNM) classification. Survival benefit for cisplatin-combinations has been quantified at about 5.4% at 5 years by the Lung Adjuvant Cisplatin Evaluation (LACE) meta-analysis [1]. In another meta-analysis, Burdett et al. reported an absolute increase in survival at 5 years of about 4% [2]. Overall survival rates at 5 years range from 90% to 12% according to the stage at diagnosis (from IA to IIIC) [3].

CT has remained the only therapeutic standard-of-care option in the adjuvant setting for almost two decades. Only in most recent years, with the revolution of immunotherapy and new targeted therapies for oncogene-addicted disease in the advanced setting, the opportunity to exploit the possible benefit deriving from these new treatment options in earlier stages has been taken into consideration. In this way, while molecular testing and Programmed death-ligand 1 (PD-L1) evaluation have become mandatory over the years in advanced NSCLC to identify predictive factors for new therapies, it has not been historically required as a routine in stage I-III disease: it represents only a recent addiction in early-stage NSCLC patients (pts) due to the several clinical trials conducted both in the adjuvant and neoadjuvant setting.

Recent trials have been testing the efficacy both of driver mutation-specific tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors (ICIs) (**Figure 1**). As already happened in the advanced setting, for oncogene-addicted disease, experimentations have focused on Epidermal Growth Factor Receptor (EGFR) gene mutations (EGFRm) and Anaplastic Lymphoma Kinase (ALK) rearrangements (ALKr), the most commonly detected in NSCLC pts. It has been reported that the prevalence of EGFRm is mostly preserved throughout disease history, with a similar prevalence in early and advanced diseases [4]. On the contrary, ALKr tend to be reported as less frequent in earlier stages [5][6], probably as a consequence of a more aggressive clinical behavior with rapidly developing metastases. Therefore, EGFRm are expected in up to 15% of early-stage NSCLC Caucasian pts, while ALKr can be found in less than 5% of them.

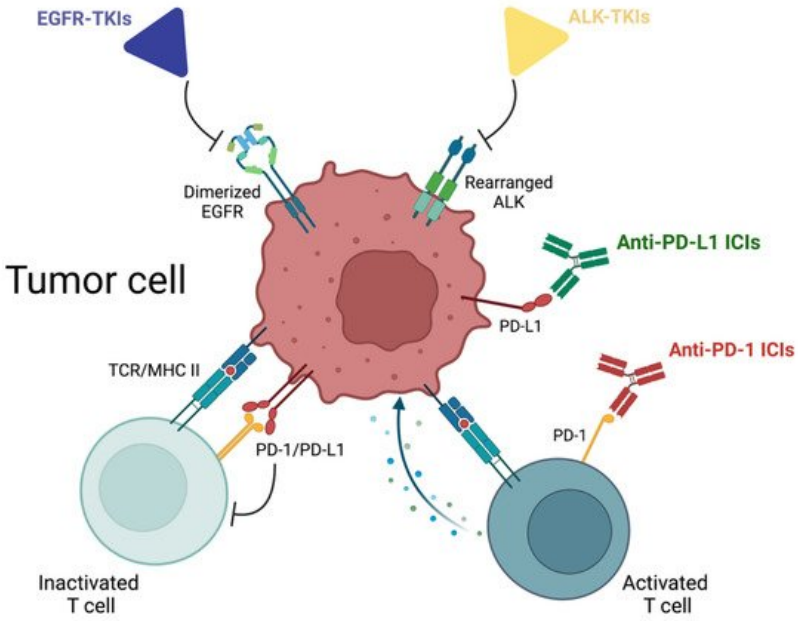

Figure 1. Mechanisms of action of main drugs evaluated in the adjuvant and neoadjuvant setting in NSCLC patients (created with BioRender.com (accessed on 15 June 2022)). *Abbreviations: EGFR, Epidermal Growth Factor Receptor; ALK, Anaplastic Lymphoma Kinase; TKIs, tyrosine kinase inhibitors; PD-(L)1, Programmed death-(ligand) 1; ICIs, immune checkpoint inhibitors; TCR, T-cell receptor; MHC II, major histocompatibility complex*.

Far less common are ROS Proto-Oncogene 1 (ROS1), RET or Neurotrophic Tyrosine Receptor Kinase (NTRK) 1–3 genes rearrangements, or BRAF, HER2 or MET gene alterations. All these drivers, as well as the more common KRAS gene mutations, have not been a specific focus of research yet for phase III clinical trials in early-stage NSCLC.

As regards immunotherapy trials, pharmacological agents have been variably tested both considering and irrespective of PD-L1 evaluation on tumor cells.

In the numerous completed or still ongoing trials with TKIs and ICIs, drugs have been experimented with after standard platinum-based adjuvant CT or as a replacement to it. This still remains an open question, whether postoperative CT can be actually superseded in biomarker-selected pts candidates to adjuvant new generation therapies.

2. EGFR Tyrosine Kinase Inhibitors

2.1. Adjuvant Setting

It is reported that pts with common EGFR mutations (exon 19 deletion (Ex19del) and exon 21 L858R mutation) typically have a shorter DFS after radical surgery, even if receiving standard platinum-based adjuvant CT [7]. Also considering the poorer prognosis of these pts, several clinical trials have explored the DFS benefit of EGFR-TKIs in the adjuvant setting.

The BR19 trial (NCT00049543) was the first phase III trial to evaluate **gefitinib**, a first-generation EGFR-TKI [8]. 503 pts with stage IB-IIIA resected NSCLC and not selected by EGFRm received either oral gefitinib 250 mg die or placebo for up to 2 years after postoperative radiotherapy and eventual CT. No benefit was reported, neither in DFS (HR 1.22, 95% CI 0.93–1.61, $p = 0.15$), nor in overall survival (OS) (HR 1.24, 95% CI 0.94–1.64, $p = 0.14$). No benefit was evidenced also in the small subgroup of EGFRm pts (4 out of 359 with known EGFR status). The trial was prematurely closed (an enrollment of 1242 pts had been planned).

The phase III ADJUVANT-CTONG1104 trial (NCT01405079) enrolled 222 pts with resected stage II-IIIA EGFRm NSCLC [9]. They were randomized to gefitinib 250 mg die for 2 years or standard adjuvant CT with cisplatin-vinorelbine for 4 cycles. Median DFS was significantly longer in the experimental arm (30.8 vs. 19.8 months (m), HR 0.56, 95% CI 0.40–0.79, $p = 0.001$), with a DFS rate at 3 and 5 years of 39.6% vs. 32.5% and 22.6% vs. 23.2%, respectively. The benefit in DFS did not translate to survival, with a not statistically significant OS advantage (median of 75.5 vs. 62.8 m, HR 0.92, 95% CI 0.62–1.36, $p = 0.674$). Subsequent treatments received after disease relapse mostly contributed to OS (median not reached with other treatments received vs. 62.8 m with no other lines), especially if subsequent EGFR-TKIs were used (HR 0.23).

The phase III IMPACT trial (UMIN000006252) randomized 234 pts with stage II-III EGFRm NSCLC to 2 years of gefitinib or standard adjuvant CT [10]. The experimental arm showed a numerical benefit in DFS which was not statistically significant (median of 35.9 vs. 25.1 m, HR 0.92, 95% CI 0.67–1.28, *p* = 0.63); DFS rates at 5 years were 31.8% and 34.1% in the two arms. No difference in OS was reported (HR 1.03, 95% CI 0.65–1.65, *p* = 0.89; OS rates at 5 years 78.0% vs. 74.6%).

RADIANT phase III trial (NCT00373425) evaluated the benefit from another first-generation EGFR-TKI, **erlotinib** [11]. 973 stage IB-IIIA pts with EGFR-expressing tumors (either ≥ 1% staining at immunohistochemistry (IHC) or gene amplification at fluorescence in situ hybridization (FISH)) were randomized to erlotinib 150 mg die or placebo for 2 years after adjuvant CT. No significant difference in DFS (median of 50.5 vs. 48.2 m, HR 0.90, 95% CI 0.74–1.10, *p* = 0.324) and OS (median not reached, HR 1.13, 95% CI 0.88–1.45, *p* = 0.335) was reported between treatment arms. 161 pts (16.5%) were EGFRm and a DFS benefit was observed in this subgroup (median of 46.4 vs. 28.5 m, HR 0.61, 95% CI 0.38–0.98, *p* = 0.039), even if not statistically significant due to the hierarchical structure of the trial. Also, the phase II trial SELECT (NCT00567359) experimented erlotinib in stage IA-IIIA NSCLC pts [12]. 100 pts with EGFRm received erlotinib for 2 years, after adjuvant CT and eventual radiotherapy. Median DFS and OS were not reached, with 5-year DFS and OS rates of 56% (95% CI 45–66) and 86% (95% CI 77–92), respectively. The primary endpoint was a 10% improvement of the 2-year DFS rate in comparison to historical control, which was reached (88% vs. 76%, *p* = 0.0047).

EVAN (NCT01683175, phase II) assessed erlotinib in resected EGFRm NSCLC pts with stage IIIA only [13]. 102 pts were randomized to erlotinib for 2 years or standard adjuvant CT, with a reported benefit in DFS rate at 2 years of 36.7% (95% CI 15.5–58.0, *p* = 0.0007), 81.4% vs. 44.6% in the two arms, respectively (RR 1.82, 95% CI 1.19–2.78, *p* = 0.0054); median DFS was 42.4 vs. 21.0 m (HR 0.27, 95% CI 0.14–0.53, *p* < 0.0001). At a following update [14], a benefit was described also for OS (median of 84.2 vs. 61.1 m, HR 0.32, 95% CI 0.15–0.67), with a 5-year OS rate of 84.8% vs. 51.1%.

The possible benefit derived from **icotinib**, another EGFR-TKI, was evaluated in the EVIDENCE trial (NCT02448797, phase III), in which 322 stage II-IIIA EGFRm NSCLC pts were randomized to icotinib 125 mg × 3 die for 2 years or standard CT [15]. A DFS benefit was evidenced, with a median of 47.0 vs. 22.1 m (HR 0.36, 95% CI 0.24–0.55, *p* < 0.0001) and a 3-year DFS rate of 63.9% vs. 32.5%. Data on OS are still immature (HR 0.91, 95% CI 0.42–1.94).

Finally, ADAURA (NCT02511106) is a phase III trial in which 682 stage IB-IIIA EGFRm NSCLC pts were randomized to receive either **osimertinib** 80 mg die orally or placebo for up to 3 years, after having received or not adjuvant CT [16][17]. Considering stage II-IIIA pts only (470, i.e., 69%), in which DFS benefit was evaluated as the primary endpoint, median DFS was not reached but an 83% risk reduction for disease relapse or death was evidenced (HR 0.17, 99% CI 0.11–0.26, *p* < 0.001) at an interim analysis. DFS benefit was maintained also in the overall population (HR 0.20, 99% CI 0.14–0.30, *p* < 0.001) and was independent of disease stage and from having received adjuvant CT (60% of pts) or not (HR 0.16 with 95% CI 0.10–0.26 and HR 0.23 with 95% CI 0.13–0.40, respectively). OS data were immature, with a 2-year OS rate of 98% vs. 85%. A significant reduction in central nervous system (CNS) recurrence was reported in the experimental arm (HR 0.18, 95% CI 0.10–0.33).

In all the aforementioned trials enrolling EGFRm pts, common mutations (Ex19del and exon 21 L858R mutation) were considered. Data from all the completed/concluding clinical trials with EGFR-TKIs in the adjuvant setting are summarized in **Table 1**.

Table 1. Clinical trials with available data with EGFR-TKIs in the adjuvant setting.

Clinical Trial	Phase	N° pts [a]	Years	Stage	Treatment Arms	DFS	OS
BR19 [8] (NCT00049543)	**III**	**503 (EGFRm-unselected)**	**2002–2005**	**IB-IIIA**	**Gefitinib × 2 y vs. placebo (after adj CT) (1:1)**	**No difference (HR 1.22, 95% CI 0.93–1.61, *p* = 0.15)**	**No difference (HR 1.24, 95% CI 0.94–1.64, *p* = 0.14)**
ADJUVANT-CTONG1104 [9] (NCT01405079)	**III**	**222**	**2011–2014**	**II-IIIA**	**Gefitinib × 2 y vs. adj CT (1:1)**	**30.8 vs. 19.8 m (HR 0.56, 95% CI 0.40–0.79, *p* = 0.001)**	**75.5 vs. 62.8 m (HR 0.92, 95% CI 0.62–1.36, *p* = 0.674)**
IMPACT [10] (UMIN000006252)	**III**	**234**	**2011–2015**	**II-III**	**Gefitinib × 2 y vs. adj CT (1:1)**	**35.9 vs. 25.1 m (HR 0.92, 95% CI 0.67–1.28, *p* = 0.63)**	**No difference (HR 1.03, 95% CI 0.65–1.65, *p* = 0.89)**

Clinical Trial	Phase	N° pts [a]	Years	Stage	Treatment Arms	DFS	OS
RADIANT [11] (NCT00373425)	III	973 ('EGFR-positive')	2007–2010	IB-IIIA	Erlotinib × 2 y vs. placebo (after adj CT) (2:1)	50.5 vs. 48.2 m (HR 0.90, 95% CI 0.74–1.10, *p* = 0.324)	Not reached (HR 1.13, 95% CI 0.88–1.45, *p* = 0.335)
SELECT [12] (NCT00567359)	II	100	2008–2012	IA-IIIA	Erlotinib × 2 y (after adj CT)	Not reached (5-year DFS rate 56%)	Not reached (5-year OS rate 86%)
EVAN [13][14] (NCT01683175)	II	102	2012–2015	IIIA	Erlotinib × 2 y vs. adj CT (1:1)	42.4 vs. 21.0 m (HR 0.27, 95% CI 0.14–0.53, *p* < 0.0001)	84.2 vs. 61.1 m (HR 0.32, 95% CI 0.15–0.67)
EVIDENCE [15] (NCT02448797)	III	322	2015–2019	II-IIIA	Icotinib × 2 y vs. adj CT (1:1)	47.0 vs. 22.1 m (HR 0.36, 95% CI 0.24–0.55, *p* < 0.0001)	Not reached (HR 0.91, 95% CI 0.42–1.94)
ADAURA [16][17] (NCT02511106)	III	682	2015–2019	IB-IIIA	Osimertinib × 3 y vs. placebo (after adj CT or not) (1:1)	Not reached vs. 27.5 m (HR 0.20, 99% CI 0.14–0.30, *p* < 0.001) [b]	Not reached (2-year OS rate 98% vs. 85%) [b]

[a] Patients where EGFRm were not specified. [b] Data regarding overall population. *Abbreviations: EGFR-TKIs, Epidermal Growth Factor Receptor tyrosine kinase inhibitors; N° pts, number of patients; DFS, disease-free survival; OS, overall survival; EGFRm, EGFR mutations; y, years; adj, adjuvant; CT, chemotherapy; m, months.*

Several clinical trials with EGFR-TKIs in the adjuvant setting are currently ongoing (**Table 2**), evaluating the survival benefits both from first-, second-, or third-generation TKIs (i.e., gefitinib, erlotinib, icotinib, afatinib, osimertinib) and new molecules (i.e., furmonertinib, almonertinib).

Table 2. Ongoing clinical trials with EGFR-TKIs in the adjuvant setting.

Clinical Trial	Phase	N° pts	Estimated Primary Completion	Stage	Treatment Arms	Primary Endpoint
NCT02518802	III	220	Jan 2018	II-IIIA	Gefitinib × 2 y started during or after CT vs. adj CT	DFS
NCT03381430	II	50	Mar 2023	IIIA N2	Gefitinib × 2 y + adj RT	DFS
NCT02193282	III	450 [a]	Oct 2026	IB-IIIA	Erlotinib × 2 y vs. placebo (after adj CT)	OS
ICWIP [18] (NCT02125240)	III	124	Dec 2018	II-IIIA	Icotinib × 3 y vs. placebo	DFS
ICTAN (NCT01996098)	III	318	Jan 2020	II-IIIA	Icotinib × 6 m vs. icotinib × 12 m vs. observation (after adj CT)	DFS
NCT03983811	III	174	Oct 2021	IIB-IIIA	Icotinib/placebo on days 8–15 during adj q21 CT cycles, then × 2 y	DFS
CORIN (NCT02264210)	II	128	Dec 2025	IB	Icotinib × 12 m vs. observation	DFS
NCT01746251	II	92	Nov 2020	I-III	Afatinib × 3 m vs. afatinib × 2 y	RFS
ADAURA2 (NCT05120349)	III	380	Aug 2027	IA2-IA3	Osimertinib × 3 y vs. placebo	DFS
FORWARD (NCT04853342)	III	318	Dec 2023	II-IIIA	Furmonertinib vs. placebo (after adj CT)	DFS
ATHEM (NCT05165355)	II	90	Nov 2024	IB-IIA [b]	Furmonertinib × 3 y	DFS

Clinical Trial	Phase	N° pts	Estimated Primary Completion	Stage	Treatment Arms	Primary Endpoint
NCT04687241	III	192	Jan 2026	II-IIIB N2	Almonertinib vs. placebo (after adj CT)	DFS
APEX (NCT04762459)	III	606	May 2026	II-IIIA	Almonertinib × 3 y vs. almonertinib + adj CT vs. adj CT (3:2:1)	DFS

[a] Trial arm with EGFRm patients. [b] Patients with high-risk pathological subtypes. *Abbreviations: EGFR-TKIs, Epidermal Growth Factor Receptor tyrosine kinase inhibitors; N° pts, number of patients; y, years; CT, chemotherapy; adj, adjuvant; DFS, disease-free survival; RT, radiotherapy; OS, overall survival; m, months; RFS, recurrence-free survival.*

Considering the available literature data from trials with concluded enrollment and completed or interim analyses, different EGFR-TKIs have shown a DFS benefit in EGFRm pts in comparison to standard adjuvant CT or as an addition to CT alone: gefitinib for 2 years after CT (ADJUVANT-CTONG1104), erlotinib for 2 years both after (SELECT, even if phase II and with immature data) or instead of CT (EVAN, phase II), icotinib for 2 years instead of CT (EVIDENCE), osimertinib for 3 years possibly after CT (ADAURA). However, no phase III trial has shown an OS benefit yet, with particular reference to all the trials with gefitinib, which already have mature data.

Several discussions have been made on the effective capacity of EGFR-TKIs to actually prevent disease recurrence, rather than simply delaying it. Keeping the focus on gefitinib, the DFS benefit appeared as a minimum, with disease relapse within 1 median year from experimental therapy completion; treatment arms had Kaplan-Meier survival curves crossing around 4 years after surgery and similar 5-year DFS rates (31.8% vs. 34.1% in IMPACT, 22.6% vs. 23.2% in ADJUVANT-CTONG1104). From these considerations, also a question on which is the optimal EGFR-TKI treatment duration arises, examining the brief disease-free interval after therapy interruption. ADAURA has been the only trial in which the adjuvant targeted therapy has been prolonged from 2 to 3 years.

Distinct meta-analyses have analyzed the comprehensive data and survival benefits with the different EGFR-TKis. Yin et al. [19] considered 11 studies with a total of 1900 EGFRm pts included and reported a DFS benefit with an HR of 0.42 (95% CI 0.31–0.57) and an OS benefit with an HR of 0.62 (95% CI 0.45–0.86). Chen et al. [20], with 7 randomized clinical trials considered and 1283 EGFRm pts included, reported similar data for DFS benefit (HR 0.41, 95% CI 0.24–0.70, p = 0.001) but no statistically significant OS benefit (HR 0.72, 95% CI 0.37–1.41, p = 0.336).

The published data with osimertinib certainly appear encouraging, with an unprecedented benefit in terms of DFS: an HR of 0.17 in the population considered for the primary endpoint and of 0.20 in the overall population. ADAURA also presented an important reduction in CNS recurrence in comparison to other EGFR-TKIs, which is coherent with the known superior CNS activity of osimertinib [21]. In this way, considering efficacy and safety data, ADAURA brought to a change in clinical practice, with the Food and Drug Administration (FDA) and European Medicines Agency (EMA) approval of osimertinib as the first targeted therapy available in the adjuvant setting for NSCLC pts. Longer follow-up and OS data maturity are anyway expected to confirm the magnitude of its effectiveness.

Since ADAURA allowed osimertinib administration both with and without previous adjuvant CT (and DFS benefit appeared as independent from CT) and considering that other trials showing DFS benefit (ADJUVANT-CTONG1104, EVAN, EVIDENCE) used EGFR-TKIs without CT, there is still no conclusive answer to whether these drugs should be employed with or without other antineoplastic agents.

2.2. Neoadjuvant Setting

The already available published data in the neoadjuvant setting derive from small phase II trials with first-generation EGFR-TKIs. NCT00188617 [22] was the first one to evaluate neoadjuvant **gefitinib** for 28 days in 36 stage I NSCLC pts non selected for EGFRm. In NCT00600587 [23], stage IIIA(N2) EGFRm pts were assigned to neoadjuvant **erlotinib** while pts without EGFRm received only CT. Objective response rate (ORR) was numerically higher in the experimental arm (58.3% vs. 25.0%). Also NCT01217619 [24] evaluated neoadjuvant erlotinib in the same setting of stage IIIA(N2) EGFRm pts, with a reported ORR of 42.1%.

In the EMERGING-CTONG1103 (NCT01407822) phase II trial [25], neoadjuvant erlotinib was compared with carboplatin-gemcitabine CT in stage IIIA EGFRm pts, with the possibility to continue the same therapy in each treatment arm also in the adjuvant setting. The 3-year and 5-year OS rates were 58.6% vs. 55.9% (p = 0.819) and 40.8% vs. 27.6% (p = 0.252), respectively.

Other trials are assessing the efficacy of targeted therapy started in the neoadjuvant setting and possibly continued even after surgery (**Table 3**). In particular, NeoADAURA (NCT04351555) is evaluating the benefit from neoadjuvant **osimertinib**, both in combination with CT for 3 cycles and alone for at least 9 weeks, in comparison to standard CT. CT and/or osimertinib can then be considered also in the adjuvant setting.

Table 3. Ongoing clinical trials with EGFR-TKIs in the neoadjuvant (+adjuvant) setting.

Clinical Trial	Phase	N° pts	Estimated Primary Completion	Stage	Treatment Arms	Primary Endpoint
NCT03656393	III	48	Jul 2020	II-IIIA	Gefitinib × 56 d vs. CT × 6 w (+ adj CT if not responding disease)	2-year DFS rate
NCT03203590	III	590	Jan 2026	II-IIIA	Gefitinib × 8 w vs. CT × 2 cycles	2-year DFS rate
NCT03749213	II	36	Feb 2022	IIIA N2	Neoadj icotinib × 8 w, then × 2 y after surgery	ORR
Neoafa (NCT04470076)	II	30	Dec 2021	II-IIIB	Neoadj CT + afatinib (48 h after and until 24 h before CT) × 3 cycles, then adj afatinib × 2 y after surgery	MPR, ORR
NCT03433469	II	27	Dec 2022	I-IIIA	Neoadj osimertinib × 1–2 cycles	MPR
NeoADAURA [26] (NCT04351555)	III	328	Mar 2024	II-IIIB N2	Neoadj osimertinib + CT × 3 cycles vs. placebo + CT vs. osimertinib alone (1:1:1)	MPR

Abbreviations: EGFR-TKIs, Epidermal Growth Factor Receptor tyrosine kinase inhibitors; N° pts, number of patients; d, days; w, weeks; CT, chemotherapy; adj, adjuvant; DFS, disease-free survival; y, years; ORR, objective response rate; neoadj, neoadjuvant; MPR, major pathological response.

3. ALK Tyrosine Kinase Inhibitors

As described for EGFRm pts, it has been reported that also ALKr are associated with a worse prognosis in resected NSCLC pts [27][28]. However, literature data are not univocal and even if ALKr tumors are described as clinically aggressive, often with lymph nodes involvement despite low T stage [29], the effective prognostic significance of ALKr in resected NSCLC remains unsettled [5][30][31].

In comparison to the EGFRm disease, far less clinical trials have been investigating the role of specific TKIs in the ALKr early disease, with no currently published data available. Several trials are presently ongoing (**Table 4**).

Table 4. Ongoing clinical trials with ALK-TKIs in the (neo-)adjuvant setting.

Clinical Trial	Phase	N° pts	Estimated Primary Completion	Stage	Treatment Arms	Primary Endpoint
ALCHEMIST [32] (NCT02194738)	III	8300 [a]	Sep 2026	IB-IIIA	Crizotinib × 2 y vs. observation (after adj CT)	OS
ALINA [33] (NCT03456076)	III	257	Jun 2023	IB-IIIA	Alectinib × 2 y vs. adj CT	DFS
NCT05341583	III	202	Jun 2025	II-IIIB	Ensartinib × 2 y vs. placebo	DFS
NCT05186506	II	152	Dec 2025	II-IIIA	Ensartinib × 2 y vs. adj CT	DFS
NCT05241028	II	80	Feb 2027	IB-IIIA	Ensartinib × 3 y (after adj CT)	3-year DFS rate
ALNEO [34] (NCT05015010)	II	33	May 2023	III	Neoadj alectinib × 8 w, then adj × 96 w after surgery	MPR
NAUTIKA1 (NCT04302025)	II	80 [a]	Mar 2023	IB-III	Neoadj alectinib × 8 w, then adj CT and alectinib × 2 y	MPR

[a] Population for the whole trial, independently from oncogenic drivers. *Abbreviations: ALK-TKIs, Anaplastic Lymphoma Kinase tyrosine kinase inhibitors; N° pts, number of patients; y, years; adj, adjuvant; CT, chemotherapy; OS, overall survival; DFS, disease-free survival; neoadj, neoadjuvant; w, weeks; MPR, major pathological response.*

ALCHEMIST (NCT02194738) is a large phase III trial in which 8300 pts with resected stage IB-IIIA NSCLC are tested for gene driver alterations in order to optimize their adjuvant treatment with targeted therapies [32]. Pts in the ALKr arm are being randomized to **crizotinib** 250 mg × 2 die for 2 years or observation after standard adjuvant CT.

Phase III ALINA trial (NCT03456076) is randomizing stage IB-IIIA ALKr NSCLC pts to either **alectinib** 600 mg × 2 die for 2 years or adjuvant CT [33].

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