Review Article

Early-stage anaplastic lymphoma kinase (*ALK*)-positive lung cancer: a narrative review

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Background and Objective: While anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitors (TKIs) are standard of care treatment for metastatic *ALK*-positive non-small cell lung cancer (NSCLC), the benefit of moving ALK inhibitors to earlier disease stages is unclear. The objective of this review is to summarize the literature regarding the prevalence and prognosis of early-stage *ALK*-positive NSCLC and the utility of targeted therapies, immunotherapy, and chemotherapy in the neoadjuvant and adjuvant settings.

Methods: We identified the references for this narrative review through a literature search of papers about early stage *ALK*-positive NSCLC using PubMed and clinicaltrials.gov. Last search was run on July 3, 2022. There were no language or time frame restrictions.

Key Content and Findings: The incidence of oncogenic *ALK* alterations in early-stage NSCLC ranges from 2–7%, and *ALK*-positive NSCLC patients are more likely to be younger and never or light smokers. Studies on the prognostic impact of *ALK* in early-stage disease have had conflicting results. ALK TKIs are not approved in the neoadjuvant or adjuvant setting and there is a lack of large, randomized trial results. Several trials are currently accruing but results are not expected for several years.

Conclusions: Attempts at large, randomized trials to evaluate the benefit of ALK TKIs in the adjuvant and neoadjuvant has been hampered by slow recruitment given the rarity of *ALK* alterations, lack of universal genetic testing, and the rapid pace of drug development. Expanded lung cancer screening recommendations, liberalization of surrogate endpoints (i.e., pathological complete response and major pathological response), growth of multicenter national clinical trials, and new diagnostic technologies (i.e., cell-free DNA liquid biopsies) provide hope of generating much needed data to definitively answer the question of the utility of ALK-directed therapies in the early-stage setting.

Keywords: Anaplastic lymphoma kinase (ALK); non-small cell lung cancer (NSCLC); tyrosine kinase inhibitor (TKI); early-stage

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Introduction

Background

Non-small cell lung cancer (NSCLC) remains the leading cause of cancer-related deaths with over two million new lung cancer cases per year globally (1). The incidence of stage I NSCLC has increased from 10.8 to 13.2 per 100,000 in the United States (2). There has also been a shift in treatment trends for patients with early stage NSCLC: fewer patients are solely receiving surgery as treatment for stage I-IIIA (2). Comprehensive genomic sequencing has transformed the treatment of NSCLC, enabling the use of highly effective targeted therapies in the metastatic setting (3-6). However, aside from osimertinib for patients with

Table 1 The search strategy summary

Items	Specification
Date of search	7/3/2022
Databases and other sources searched	PubMed, clinicaltrials.gov
Search terms used	(non-small cell lung cancer) AND (ALK) AND ((early stage) OR (stage III) OR (stage II) OR (stage I))
Timeframe	No restrictions
Inclusion and exclusion criteria	No language restrictions, all study types
Selection process	One MD conducted the selection (MC)

ALK, anaplastic lymphoma kinase.

resected stage IB-III epidermal growth factor receptor (*EGFR*) mutated NSCLC, the benefit of such agents in earlier stage disease is unclear (7).

Anaplastic lymphoma kinase (*ALK*) fusions in lung cancers are rare and are found in 2–7% of NSCLC (8). Use of an increasing number of ALK tyrosine kinase inhibitors (TKIs) has significantly improved outcomes for patients with metastatic *ALK*-positive NSCLC, and many of these patients will receive multiple lines of therapeutic ALK inhibition before being considered candidates for cytotoxic chemotherapy (9).

Rationale and knowledge gap

Despite these huge therapeutic advances for patients with metastatic *ALK*-positive disease, treatment practices for early-stage *ALK*-positive NSCLC remains the same as for patients without an oncogenic driver. In early-stage NSCLC, surgery is a potentially curative approach although the recurrence rates are high. Early-stage surgically resected NSCLC has a 5-year overall survival (OS) rate ranging from 68% for stage IB disease to 26% for stage IIIB disease (10). Adjuvant chemotherapy for resected patients with stage II-III disease provides a modest survival benefit of 5% at 5 years (11). The benefit of moving ALK inhibitors to earlier stage disease seems obvious, however, limited data are available to support this approach. The rarity of *ALK* fusions and the lack of standardized genomic testing in early-stage disease has historically posed a challenge to neoadjuvant and adjuvant trials, though large initiatives are working to overcome this, including the NCI's ALCHEMIST program (NCT02194738) and the Lung Cancer Research Foundation's study to screen patients with resectable lung cancer for actionable oncogene mutations and fusions preoperatively (NCT04712877) (12,13).

Objective

The objective of this narrative review is to summarize the literature regarding the prevalence and prognosis of early-stage *ALK*-positive NSCLC and the utility of targeted therapy, immunotherapy, and chemotherapy in the neoadjuvant and adjuvant settings. While previous reviews have summarized the frequency of early-stage *ALK*-positive NSCLC and challenges in conducting adjuvant ALK inhibitor clinical trials, they were completed several years ago, during which additional clinical trials have opened and closed (14-16). We present this article in accordance with the Narrative Review reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-631/rc).

Methods

We performed a literature search for papers published in PubMed and clinicaltrials.gov up to July 3, 2022 on early-stage *ALK*-positive NSCLC. See *Table 1* for full search criteria. We did not use any date or language restrictions in the electronic searches for trials.

Baseline clinical characteristics for early-stage ALK-positive NSCLC

Historically, standardized biomarker testing was not routinely done for early-stage NSCLC, making it difficult to accurately assess the prevalence of *ALK* alterations in early-stage NSCLC. Small retrospective studies have reported varying incidences ranging from 2–7% (17-19).

Compared to *ALK*-negative lung cancer, patients with *ALK*-positive lung cancer are more likely to be younger, never or light smokers, and have a more equal gender distribution (18,20). Unlike other oncologic drivers like *EGFR*, *ALK* fusions are more frequently identified at an

advanced stage (found in 2–7% of early-stage cancers versus 19% of stage IV cancers) (19,21).

Defining the prognostic impact of *ALK* has been difficult due to the rarity of *ALK* rearrangements in the early-stage setting, the paucity of prospective data, and the use of molecularly heterogeneous comparator arms. Small retrospective studies have published conflicting results (17,18,20-31). The European Thoracic Oncology Platform Lungscape Project, one of the largest cohorts of early-stage resected stage I-III NSCLC to date, examined 80 patients with *ALK*-positive lung cancer and found that *ALK* positivity was associated with better OS [not reached (NR) for ALK IHC-positive patients *vs.* 69.5 months for ALK-IHC negative patients, HR 0.61, 95% CI: 0.41–0.90] (17). On the other hand, four separate studies reported an association between *ALK* positivity and worse disease-free survival (20,22-24). Part of this discrepancy may be secondary to smoking status and the use of different endpoints [OS *vs.* disease free survival (DFS)]. In a large meta-analysis of 4,981 patients with NSCLC, Wang *et al.* found that *ALK* rearrangements predicted a better prognosis in the general population with NSCLC but a worse prognosis in the non-smoking population (27). Two of the studies that reported worse outcomes with *ALK* positivity were comprised exclusively of never smokers while the Lungscape Project predominantly was comprised of smokers (17,22,23). This highlights the complexity of establishing the true prognostic relevance of *ALK* status in early-stage lung cancer and the importance of looking for confounders.

To characterize how outcomes differ for patients with *ALK* fusions compared with other driver mutations, Chaft *et al.* analyzed 764 patients with surgically resected stage I-III NSCLC; 29 had an *ALK* rearrangement, 255 had an *EGFR* driver mutation, and 480 had a *KRAS* mutation (18). After adjusting for stage, patients with *ALK*-positive NSCLC had worse outcomes relative to *EGFR*-mutant NSCLC (HR 1.8, 95% CI: 1.1–3.1) but not compared to *KRAS*-mutant NSCLC (HR 1.3, 95% CI: 0.8–2.1) (18).

There are limited data reporting outcomes for early-stage *ALK*-positive NSCLC stratified by stage. Recently, one small retrospective study examined 48 patients with stage I-III *ALK*-positive NSCLC at two Canadian cancer centers; 40% had stage I disease, 10% had stage II disease, and 50% had stage III disease (32). Median progression-free survival was 144.0 months for stage I disease, 27.6 months for stage II disease, 14.9 months for stage III disease, and 10.9 months for unresectable stage III disease (32). Though preliminary, these data suggest stage strongly influences patient outcomes and emphasizes the need to identify the disease at its earliest onset to improve patient outcomes.

Adjuvant TKI therapy for early-stage ALK-positive NSCLC

ALK TKIs are not FDA-approved in the early-stage adjuvant setting, and there is a lack of large, randomized trial results. There are currently two active phase III trials investigating ALK TKIs in the adjuvant setting for early-stage disease: the Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial (ALCHEMIST, NCT02201992) and ALINA (NCT03456076) trials (33,34). The ALCHEMIST trial is a randomized, double-blind placebo-controlled phase III trial including patients with stage IB-IIIA *ALK*-positive NSCLC after surgical resection (33). Patients are randomized to receive crizotinib versus observation for 24 months after completion of standard treatment (33). The primary endpoint is OS and aims to enroll 168 patients (33). Patient enrollment started in 2014 with an estimated study completion date of 2036 (33). The ALINA trial is a phase III randomized trial of patients with resected stage IB-IIIA *ALK*-positive NSCLC investigating the efficacy of two years of adjuvant alectinib versus adjuvant platinum based chemotherapy (34). This trial opened in 2018 and is active but not recruiting with anticipated completion in 2026 (34).

Clinicaltrials.gov shows one relevant adjuvant trial in the pipeline (NCT05241028) (35). A single-center study at Hebei University Hospital in China is planned to compare three years of adjuvant ensartinib to standard of care in stage IB-IIIA *ALK*-positive NSCLC (35). The primary endpoint is 3-year disease-free survival rate (35). The trial was posted to clinicaltrials.gov in February 2022 but as of September 2022 is not yet recruiting patients (35). *Table 2* summarizes the status of the current early-stage adjuvant *ALK*-positive NSCLC clinical trials.

A major limitation for the adjuvant trials above has been the pace of recruitment. The ALCHEMIST trial for instance has been open for over eight years and is not estimated to be completed for another ten years. During this time period, second generation and third generation ALK inhibitors have been developed and replaced crizotinib as standard of care—prompting the development of new clinical trials that will likely face the same inherent problems.

Table 2 Summary of early-stage *ALK*-positive NSCLC clinical trials

Trial	Study design	Control	Primary endpoint	Target enrollment	Trial dates
ALCHEMIST (33), NCT02201992	Phase III; resected stage IB (≥4 cm)-IIIA; adjuvant crizotinib ×2 years	Placebo	OS	168 patients	Start date: 8/2014; completion date: 2036
ALINA (34), NCT03456076	Phase III; resected stage IB-IIIA; adjuvant alectinib ×2 years	Platinum-based chemotherapy	DFS	257 patients	Start date: 3/2018; completion date: 2026
NCT05241028 (35)	Phase II; stage IB-IIIA; adjuvant ensartinib ×3 years	None	DFS	80 patients	Not yet recruiting
RTOG 1306 (40), NCT01822496	Phase II; unresectable stage III; neoadjuvant crizotinib ×12 weeks	Placebo	PFS	59 patients (actual enrollment 16 patients)	Start date: 11/2013; completion date: 6/2018
SAKULA (41), UMIN00017906	Phase II; resectable stage II-III; neoadjuvant ceritinib ×12 weeks	None	mPR	19 patients (actual enrollment 7 patients)	State date: 3/2015; completion date: 10/2019
ARM (42), NCT03088930	Phase II; resectable stage IA-IIIA; neoadjuvant crizotinib ×6 weeks	None	ORR	26 patients (actual enrollment 3 patients)	Start date: 3/2017; completion date: 2/2022
ALNEO (39), NCT05015010	Phase II; resectable stage III; neoadjuvant alectinib ×8 weeks followed by adjuvant alectinib ×96 weeks	None	mPR	33 patients	Start date: 8/2021; completion date: 5/2026
NAUTIKA1 (43), NCT04302025	Phase II; resectable stage IB-III; neoadjuvant alectinib ×8 weeks followed by adjuvant alectinib ×104 weeks	None	mPR	80 patients	Start date: 3/2020; completion date: 2/2029

ALK, anaplastic lymphoma kinase; NSCLC, non-small cell lung cancer; OS, overall survival; DFS, disease free survival; PFS, progression free survival; mPR, major pathologic response; ORR, objective response rate.

Neoadjuvant TKI therapy for early-stage ALK-positive NSCLC

Like in the adjuvant setting, ALK TKIs are not FDA-approved in the neoadjuvant setting for early-stage *ALK*-positive NSCLC, and there is a lack of data from large, randomized trial results. There have been some case reports and small retrospective studies supporting the use of neoadjuvant ALK directed therapy (39,41-43). Zhang *et al.*, in a small retrospective case cohort (n=11) of *ALK*-positive pathologically confirmed N2 NSCLC, reported the efficacy of neoadjuvant crizotinib (250 mg twice daily for a median duration of 30 days) (39). All patients had responses after completion of neoadjuvant therapy and were able to proceed with surgery; 91.0% received an R0 resection and two patients (18.2%) had a pathological complete response (39). In comparison, pathological complete response with neoadjuvant chemotherapy occurs in 4–10% of patients (39). However, this small retrospective study has limited scope given all patients had stage IIIA disease and were treated with crizotinib for a wide variation of time (range, 30–120 days).

Due to difficulty with accrual, a number of neoadjuvant phase II trials have been closed, including the RTOG 1306 (NCT01822496), SAKULA (UMIN00017906), and the ARM (NCT03088930) trial (40-42). The phase II SAKULA trial ultimately only enrolled seven patients, all with stage IIIA disease and was closed due to slow accrual (41). One patient withdrew from the study because of dose limiting toxicity (hepatitis) (41). This study aimed to evaluate the efficacy of neoadjuvant ceritinib 750 mg daily for 12 weeks for patients with *ALK*-positive stage II-III NSCLC (41). The reported overall response rate was 100% and six patients underwent surgical resection of which major pathological response was 57% and complete pathologic response was 28% (41). The RTOG 1306 trial sought to compare the efficacy of 12 weeks of crizotinib followed by chemoradiation versus chemoradiation alone in unresectable stage III *ALK*-positive NSCLC (40). Of 16 patients enrolled, nine were randomized to receive induction crizotinib (40). The study started in 2013 and was terminated in 2019 (40). Progression-free survival was 14.7 months in the crizotinib group versus not reached in

the control (no crizotinib) group (40). Complete or partial response was observed in 67% of the crizotinib group *vs.* 75% in the control group (40). OS was not reached in either group. While the data reported in the SAKULA trial is promising, the RTOG study failed to also show improved response rates or progression-free survival with neoadjuvant ALK targeted therapies. This discrepancy may be because the RTOG study examined crizotinib a first-generation ALK inhibitor while the SAKULA trial used ceritinib a second-generation ALK inhibitor. However, both studies are hampered by small sample sizes and further prospective trials are needed.

There are currently two ongoing phase II neoadjuvant *ALK* trials: the ALNEO (NCT05015010) and NAUTIKA1 (NCT04302025) trials (38,43). The ALNEO trial is a single arm multicenter clinical trial examining patients with stage III potentially resectable *ALK*-positive NSCLC to receive neoadjuvant oral alectinib 600 mg bid for two cycles with a total of eight weeks (38). Following surgery, patients will receive adjuvant alectinib 600 mg bid ×24 cycles (96 weeks) (38). The primary endpoint is major pathological response (38). The trial opened in 2021 and is projected to be completed in 2026. The NAUTIKA-1 trial is a single arm trial for patients with resectable stage IB-IIIA *ALK*-positive NSCLC (43). Patients will receive eight weeks of neoadjuvant alectinib followed by two years of adjuvant alectinib (43). The primary endpoints are major pathological response and complete pathologic response (43). The trial was opened in 2020 and is projected to be completed in 2029. *Table 2* summarizes the status of the previous, current, and upcoming early stage *ALK*-positive NSCLC clinical trials.

While the results of the above newly opened clinical trials are eagerly anticipated, they will face the same hurdles as the previous trials—chiefly slow recruitment given the rarity of *ALK* rearrangements and the lack of universal early-stage genetic testing. Furthermore, they will face increased competition with the expansion of trials both in the adjuvant, neoadjuvant, and neoadjuvant/adjuvant space.

Immunotherapy

The role of immunotherapy in *ALK*-positive NSCLC is unclear since patients with *ALK* alterations are excluded from most trials. Patients with oncogenic drivers have historically been excluded from immunotherapy trials given the availability of targeted therapy and the fact that the few studies that have included patients with *ALK*-positive tumors have had poor responses to immunotherapy. In the metastatic setting, there is little benefit and increased toxicity with immunotherapy for *ALK*-positive NSCLC. Results from the IMMUNOTARGET registry, a retrospective study of over 500 advanced stage patients with at least one oncogenic driver alteration receiving immunotherapy monotherapy in 24 centers from 10 countries, the overall response rate in patients with *ALK*-positive lung cancer was 0% with median progression-free survival of 2.5 months (44). Furthermore, patients were at higher risk of hepatic toxicities with ALK inhibitors after receiving immunotherapy. An observational study found a 45% incidence of grade 3 or 4 liver enzyme elevations in patients who received crizotinib and immunotherapy versus 8% in patients who received crizotinib alone (45).

In the neoadjuvant setting for patients with stage IB-IIIA NSCLC, the LCMC3 study reported a major pathological response rate of 21% with single agent atezolizumab (46). Patients with *ALK* alterations were allowed to enroll in the LCMC3 study, but did not count towards the primary efficacy endpoint. There has been lack of consistency across industry, some perioperative immunotherapy trials exclude and others include patients with *ALK* alterations.

The PACIFIC trial showed an OS benefit in patients with stage III unresectable NSCLC who received durvalumab for a year. Patients with *ALK* alterations were included. Of just four patients with known *ALK* rearrangements, the median PFS was 7.8 months, the lowest of the reported drivers (47). However, a small retrospective non-randomized study of 20 patients with stage III *ALK*-positive NSCLC reported that the nine patients who received maintenance durvalumab had a non-significant trend toward improved progression-free survival (12.5 *vs* 5.9 months, P=0.16) (32).

Most recently in March 2022, the Food and Drug administration issued the first FDA approval for neoadjuvant therapy for early-stage NSCLC based on the CheckMate 816 study. CheckMate 816 showed that for patients with resectable stage IB to IIIA NSCLC neoadjuvant nivolumab plus chemotherapy resulted in significantly longer event-free survival and more pathological complete responses than chemotherapy alone. However, patients with known *ALK* fusions were excluded (48).

Overall, there is a lack of clarity regarding the utility of immunotherapy in the early stage setting for *ALK*-positive patients and increased inclusion in trials is needed to help answer this critical question.

Limitations and future directions

This review highlights the current landscape in early-stage *ALK*-positive NSCLC. Despite impressive multicenter efforts to answer the question regarding the utility of ALK TKIs in the adjuvant and neoadjuvant setting, definitive answers have not been reached, trials have been forced to close early due to slow recruitment, and many of the active trials are not utilizing the latest generation of ALK TKIs.

The approach for early stage *ALK* trials needs to shift to avoid the enrollment challenges of previous trials. There needs to be improved screening to identify more patients when they have early-stage disease. In 2021, the US Preventive Services Task Force (USPSTF) updated the USPSTF lung cancer screening recommendations for the first time since 2013. The USPSTF liberalized the screening age to 50 years old from 55 years old and smoking history to 20 pack-years from 30 pack-years. These new guidelines are based on two large prospective trials (NELSON and LDCT) that showed that liberalizing lung cancer screening reduced the risk of dying from lung cancer by at least 20% (49-51). With this change, eight million more individuals will be eligible for screening (52). While this should increase the number of patients diagnosed with early stage versus metastatic disease, it is unclear if this will increase the incidence of early stage *ALK*-positive disease, given its increased incidence in never-smokers.

Other efforts to improve the operational challenges of perioperative trials include a shift towards surrogate endpoints (i.e., pathological complete response and major pathological response instead of event free survival for neoadjuvant studies and disease-free survival instead of OS for adjuvant studies). Historically, the length of time from enrollment until publication for perioperative treatments for NSCLC when OS was used as the primary endpoint has ranged from 9–13 years (53). Shifting to surrogate endpoints would significantly expedite results and is being used in other disease types, most notably breast cancer. Finally, the use of new diagnostic technologies like cell-free DNA liquid biopsies has expedited genomic testing results and may make universal genomic testing for early-stage disease feasible.

Summary

Current challenges and future directions

ALK-directed therapy has drastically changed the treatment landscape for patients with metastatic NSCLC, where *ALK* testing has been standard of care for years. The FDA-approval of *ALK* testing by immunohistochemistry makes identifying alterations easy and rapid. However, despite this option, attempts at large, randomized trials evaluating the utility of ALK TKIs in the adjuvant and neoadjuvant settings have been challenged by slow recruitment given the rarity of *ALK* rearrangements and the lack of universal genetic testing in the early stage. Furthermore, the rapid pace of drug development has posed barriers to ongoing perioperative trials. For example, the still recruiting ALCHEMIST study of crizotinib is testing a TKI that is no longer considered the gold standard for patients with more advanced *ALK*-positive disease.

To avoid the pitfalls of previous trials, enrollment strategies and study designs need to change. Improved screening is essential to identify more early-stage patients and ideally the updated liberalized lung cancer screening recommendations will expedite this. However, lung cancer screening uptake thus far has been poor—one study reported that out of more than 800,000 smokers eligible for lung cancer screening according to USPSTF criteria, only 16% received appropriate screening (54). It will also be crucial to increase the scope of expedited molecular testing in early-stage NSCLC, especially for neoadjuvant trials. The use of new diagnostic technologies like cell-free DNA liquid biopsies may make universal genomic testing for early-stage disease feasible. In terms of changes to perioperative trial design, a shift towards surrogate endpoints (i.e., pathological complete response and major pathological response instead of event free survival for neoadjuvant studies and disease-free survival instead of OS for adjuvant studies) could significantly expedite results. Ultimately, success of early-stage *ALK*-positive lung cancer clinical trials requires buy-in from both patients and providers to combat the traditionally low <5% clinical trial participation rates. Large scale screening studies, use of surrogate endpoints, and advances in diagnostic technologies including plasma tests will ideally help enrollment in ongoing studies to fill the data voids.

Conclusions

Despite these challenges, ongoing study of ALK-directed therapies remain essential. Biomarker-matched therapies are likely to ultimately improve outcomes in patients with *ALK*-positive disease, however, we lack the data. The limited data presented above, the markedly improved response with ALK TKIs over chemotherapy in patients with advanced

lung cancer, and most robustly, the data generated in the EGFR space with adjuvant osimertinib fuel our optimism of the benefit of ALK-directed therapies for early-stage disease in the adjuvant and neoadjuvant settings.

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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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