Lung Cancer: Targets and Therapy

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COMMENTARY

Redefining Recovery: The Transformative Impact of the ALINA Trial on Adjuvant Therapy for *ALK*-Positive Non-Small Cell Lung Cancer

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Abstract: On April 18, 2024, the Food and Drug Administration approved alectinib as an adjuvant treatment for patients with anaplastic lymphoma kinase (*ALK*)-positive non-small cell lung cancer (NSCLC) after tumor resection. This approval was grounded in the outcomes of the ALINA trial, which demonstrated that alectinib significantly enhances disease-free survival compared to traditional platinum-based chemotherapy in the adjuvant setting. The ALINA trial is notable not just for advancing ALK tyrosine kinase inhibitors (TKIs) into the adjuvant setting but also for its innovative approach of comparing them to adjuvant chemotherapy, distinguishing it from other landmark trials.

Keywords: *ALK*, NSCLC, adjuvant therapy, targeted therapy

Background

Anaplastic lymphoma kinase *(ALK)* rearrangements are found in approximately 3–5% of non-small cell lung cancer (NSCLC) cases, primarily in non-smokers or light smokers, and are typically associated with younger patients.[1] The discovery of *ALK* rearrangements has led to significant advancements in the treatment of NSCLC, particularly with the development of ALK-tyrosine kinase inhibitors (TKIs). These inhibitors have revolutionized the management of *ALK*-positive NSCLC, offering a targeted approach that has demonstrated significant improvements in survival rates for metastatic disease.

Current Treatment in the Metastatic Setting of ALK-Positive NSCLC

In the metastatic setting, ALK inhibitors like crizotinib, the first-generation ALK-TKI, have shown substantial efficacy in comparison to chemotherapy.[2] The development of second- and third-generation ALK inhibitors such as alectinib,[3] brigatinib,[4] and lorlatinib[5] has further improved patient outcomes. These newer agents provide improved central nervous system (CNS) penetration, greater potency, and better tolerability than crizotinib, making them the preferred options for initial therapy in advanced *ALK*-positive NSCLC.

Rationale for Moving ALK-TKIs to the Adjuvant Setting

The remarkable efficacy of ALK-TKIs in managing metastatic disease has encouraged their exploration in earlier disease stages, particularly in the adjuvant setting following surgical resection. This strategic shift is supported by the notion that early, targeted intervention can effectively eliminate microscopic residual disease, thereby diminishing recurrence risks and enhancing long-term survival prospects.[6,7] While adjuvant chemotherapy remains the conventional treatment for resected NSCLC, it often falls short in efficacy for patients with specific genetic profiles and is associated with

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substantial toxicity. ALK-TKIs represent a compelling alternative, with their established track record of preventing progression and managing metastases in more advanced stages.

ALINA Trial

The ALINA trial,[8] a global, Phase 3, randomized, open-label study, assessed the efficacy and safety of adjuvant alectinib compared to standard platinum-based chemotherapy in patients with completely resected, *ALK*-positive NSCLC. A total of 257 patients with stage IB (tumors ≥4 cm), II, or IIIA resected *ALK*-positive NSCLC were enrolled. Participants were randomized to receive either oral alectinib (600 mg twice daily for 24 months) or four 21-day cycles of platinum-based chemotherapy. The primary endpoint was disease-free survival, with secondary endpoints including overall survival (OS) and safety. The trial's design allowed for a robust comparison between a targeted therapy and traditional chemotherapy.

Alectinib significantly improved disease-free survival, particularly in patients with stage II or IIIA disease. At two years, 93.8% of alectinib recipients were disease-free compared to 63.0% of those who received chemotherapy. Additionally, alectinib demonstrated a marked advantage in CNS disease-free survival, highlighting its potential to manage and prevent metastases in a patient subset at high risk for CNS involvement. The safety profile of alectinib was favorable, with most adverse events being low-grade and fewer treatment discontinuations compared to chemotherapy.

Discussion

Significance and Limitations of the ALINA Trial

In the context of the ongoing evolution of adjuvant therapy in NSCLC, the ALINA trial, alongside studies like ADAURA[6] and LIBRETTO-432,[9] marks a significant stride in exploring the efficacy of TKIs in the early stages of NSCLC. Predominantly recruiting patients from Asia, where healthcare systems vary significantly and advanced diagnostic modalities like low-dose computed tomography are possibly more accessible, the study raises critical questions about the demographic and diagnostic intricacies of its cohort. Indeed, 55% were Asian, 42% were White and the rates of others including Blacks were very low. Notably, the ALINA trial has a large contingent of never-smokers. The lack of detailed demographic data on these never-smokers, including breakdowns by race and sex, limits a nuanced understanding of the trial's applicability to diverse populations.

Additionally, the trial utilized *ALK*-positive diagnostics that were either FDA-approved or bore the Conformité Européenne (CE) marking (which certifies that it has met the European Union health, safety and environmental requirements). However, the distribution of subjects identified as *ALK*-positive by each diagnostic method was not detailed. The study also permitted the use of both central and local laboratory testing modalities. These variabilities in testing approaches raises concerns about diagnostic accuracy, which could lead to false-positive identifications and consequently, affect the interpretation of the therapeutic efficacy. Consequently, this heterogeneity in patient populations may pose challenges in accurately assessing the therapeutic efficacy.

The reporting of median relative dose intensity in the trial, while indicative of the most commonly administered dosage, does not offer insights into the variability of dosing that a mean relative dose intensity could have provided. This is a stark contrast to other studies like FLAURA-2[10] and LIBRETTO-431,[11] which included mean relative dose intensity data, offering a more comprehensive view of dosage trends.

The ALINA trial's approach, while pioneering, thus encapsulates both the promise and the limitations of current adjuvant TKI trials in NSCLC. This underscores the need for more transparent reporting and broader diagnostic strategies to truly understand the potential and reach of TKIs in this setting, particularly in diverse and asymptomatic populations.

Duration of Adjuvant Alectinib

The choice of a two-year adjuvant alectinib course in ALINA was informed by balancing the desire to extend the benefits of ongoing therapy with the need to mitigate the hardships longer treatments pose for patients. This decision drew from evidence suggesting that longer therapies could potentially improve disease-free intervals in specific patient groups, yet might also lead to increased side effects and difficulties in maintaining patient adherence.[8]

Critical research gaps remain regarding the ideal length of adjuvant targeted treatments in NSCLC, influenced by risk factors like tumor genetic and molecular profiles, and the detection of minimal residual disease.[12] The trend in treatment strategies is shifting towards personalization. Anticipated research will likely delve into how the combination of chemotherapy with alectinib could enhance patient results and explore the viability of prolonging adjuvant alectinib beyond two years. These risk-adapted or more personalized investigations will be crucial in developing targeted treatment guidelines that consider the unique tumor biology and patient health dynamics.

Is It Time to Omit Adjuvant Chemotherapy?

The current National Comprehensive Cancer Network guidelines recommended adjuvant chemotherapy for high risk stage IIA NSCLC (category 2A) and strongly recommend it for stages IIB to IIIB (category 1).[13] Historically, adjuvant trials such as KEYNOTE-091[14] and ADAURA[6] have incorporated a phase where patients may receive chemotherapy before being randomized to either a study drug or placebo. This approach helps determine the incremental benefit of novel therapies over established chemotherapy regimens. Notably, in the ADAURA trial, the administration of osimertinib as adjuvant therapy in Epidermal Growth Factor Receptor (*EGFR*)-mutant NSCLC resulted in a remarkable two-year disease-free survival (DFS) rate of 89%, irrespective of prior chemotherapy usage.[6,7,15] These results prompt a reevaluation of the essentiality of traditional chemotherapy when highly effective targeted therapies are available, especially if such therapies alone can markedly enhance DFS while minimizing toxicity.

Further advancing this debate, the ALINA trial directly juxtaposed adjuvant targeted therapy with chemotherapy, showcasing alectinib's robust efficacy in adjuvant settings for *ALK*-positive NSCLC. Notably, alectinib effectively prolonged disease-free and CNS disease-free survival, indicating its superior capability to prevent brain metastases—a frequent complication in *ALK*-positive NSCLC that conventional chemotherapy, limited by poor penetration of the blood-brain barrier, fails to address adequately.

A significant argument for excluding traditional adjuvant chemotherapy stems from the considerable reduction in treatment-related toxicity. Alectinib, known for its favorable side effect profile, contrasts sharply with the severe toxicities often seen with platinum-based chemotherapy, potentially enhancing overall patient quality of life. This includes fewer treatment interruptions and a lower incidence of severe complications. Simplification of treatment protocols is another advantage of using alectinib as the sole adjuvant therapy. The oral administration of alectinib offers a less invasive, more convenient alternative to the intravenous delivery required for chemotherapy, easing both psychological and physical burdens on patients.

However, some may argue that patients with heterogeneous *ALK*-rearranged tumors, particularly those with co-alterations, might benefit from the cytotoxic effects of chemotherapy. The presence of co-alterations can sometimes confer resistance to targeted therapies alone, making the combination with chemotherapy potentially more effective. Chemotherapy has a broad mechanism of action that can target various cell populations within the tumor,[16] potentially reducing the risk of recurrence in cases where targeted therapy might miss certain subclones of cancer cells. Further research is needed to investigate which patient groups could benefit from adjuvant chemotherapy. Overall, the encouraging outcomes from trials like ALINA and ADAURA could shift the paradigm towards omitting adjuvant chemotherapy in favor of adopting adjuvant TKIs in patients with resected NSCLC harboring *EGFR* mutations or *ALK* fusions, promoting a move towards more personalized, less burdensome cancer care.

Exploring Perioperative Design in Future Trials

The integration of immune checkpoint inhibitors across different cancer treatment stages signifies a transformative evolution in oncological care, especially in NSCLC. Notably, the CheckMate 816 trial highlighted the promise of nivolumab, an anti-programmed death-1 (PD-1) antibody, in combination with chemotherapy, in a neoadjuvant context—administered before surgical intervention.[17] The trial reported enhanced pathological complete response rates, showcasing the benefits of early immune system engagement. Also important to note is the fact that CheckMate 816 excluded NSCLC patients without *EGFR* mutation and *ALK*-rearrangement.

Expanding on this, the Keynote 671 trial investigated pembrolizumab, another anti-PD-1 antibody, with chemotherapy, within a perioperative framework, which includes both pre- and post-operative phases.[18] Unlike CheckMate 816,

EGFR and *ALK* was not an exclusion criteria for Keynote 671 and it included a small number of such subsets, although the benefit these patients may have had is questionable.

The success of alectinib in the adjuvant setting for *ALK*-positive NSCLC raises the question of its potential effectiveness in the neoadjuvant phase. Given the advantages observed with post-operative targeted therapy, there is a compelling rationale to explore whether earlier administration of alectinib could diminish tumor burden and eradicate micro-metastases, potentially enhancing surgical results and diminishing recurrence risks.

Drawing parallels with the outcomes from the Keynote 671 trial, it is reasonable to propose that an early intervention with alectinib could confer similar, or superior, benefits, in *ALK*-positive patients. Future studies should aim to dissect the comparative effectiveness of neoadjuvant versus adjuvant vs both neoadjuvant and adjuvant alectinib, through meticulously designed trials. Examining the tumor biology in response to early alectinib treatment could unveil resistance mechanisms and inform potential synergies with other treatments like chemotherapy, thereby optimizing the therapeutic landscape for *ALK*-positive NSCLC.

How About Lorlatinib?

The findings from the CROWN study[5] have significantly bolstered the clinical promise of lorlatinib, a third-generation ALK inhibitor. In this study, lorlatinib notably outperformed crizotinib, with a median progression-free survival (PFS) not yet reached, compared to 9.3 months for crizotinib. In patients with baseline brain metastases, lorlatinib significantly delayed intracranial progression compared to crizotinib, with a hazard ratio (HR) of 0.10 (95% CI 0·04–0·27). In those without baseline brain metastases, the HR was even lower at 0.02 (95% CI 0·002–0·14), indicating a stronger benefit for lorlatinib.

The implications of these findings are profound, especially with the potential for extending the use of lorlatinib into the early disease stage (NCT05740943).[19] While lorlatinib may be a more efficacious TKI compared to alectinib, it is generally associated with a higher incidence of side effects. Consequently, a risk-adapted approach that employs lorlatinib in patients with higher risk profiles could be considered. Concurrently, the development of fourth-generation ALK inhibitors, such as NVL-655,[20] is advancing and holds the potential to significantly enrich the therapeutic landscape for *ALK*-positive NSCLC. It is imperative, however, that ongoing and future studies ensure comprehensive follow-up to allow OS data to mature, thereby providing a robust basis for evaluating the long-term efficacy and safety of these novel agents.

Conclusions

The approval of alectinib for adjuvant treatment in *ALK*-positive NSCLC represents a significant shift towards targeted therapies in early disease stages, as underscored by the ALINA trial. By demonstrating superior DFS and lower toxicity compared to conventional chemotherapy, alectinib sets a new standard in the management of resected NSCLC. This pivotal change not only enhances patient quality of life but also prompts a reevaluation of adjuvant treatment paradigms, potentially leading to more personalized, effective cancer care strategies. Future research should continue to explore a personalized, or more of a risk adaptive approach, which includes the question in regards to optimal duration of therapy with longer therapy perhaps in higher risks, and the consideration of intensification with the addition of chemotherapy in some subsets, also evaluation of the integration of such targeted treatments in the perioperative (neoadjuvant and adjuvant) setting as well.

Abbreviations

ALK, Anaplastic Lymphoma Kinase; CNS, Central Nervous System; DFS, Disease-Free Survival; EGFR, Epidermal Growth Factor Receptor; NSCLC, Non-Small Cell Lung Cancer; OS, Overall Survival; PD-1, Programmed Death-1; PFS, Progression-Free Survival; TKI, Tyrosine Kinase Inhibitor.

Ethics Statement

This commentary is based on publicly available, de-identified clinical trial data and does not require IRB approval.

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