Editorial Commentary

Targeting a cure in anaplastic lymphoma kinase-positive non-small cell lung cancer

Marie-Frédérique D'Amours^, Cheryl Ho

Department of Medical Oncology, BC Cancer Agency, Vancouver, Canada

Correspondence to: Marie-Frédérique D'Amours, MD. Department of Medical Oncology, BC Cancer Agency, 600 West 10th Avenue, Vancouver, BC V5Z 4E6, Canada. Email: marie.damours@bccancer.bc.ca.

Comment on: Wu YL, Dziadziuszko R, Ahn JS, *et al*. Alectinib in Resected ALK-Positive Non-Small-Cell Lung Cancer. N Engl J Med 2024;390:1265-76.

Keywords: Lung cancer; anaplastic lymphoma kinase (ALK); alectinib; ALK inhibitor; early-stage non-small cell lung cancer (early-stage NSCLC)

Submitted Sep 18, 2024. Accepted for publication Dec 04, 2024. Published online Dec 27, 2024.
doi: 10.21037/tlcr-24-844
View this article at: https://dx.doi.org/10.21037/tlcr-24-844

In the phase III trial "Alectinib in Resected ALK-Positive Non-Small-Cell Lung Cancer", Wu *et al.* demonstrated that 2 years of adjuvant alectinib, an anaplastic lymphoma kinase (ALK) inhibitor, was associated with a marked improvement in disease-free survival (DFS) compared to standard adjuvant platinum-based chemotherapy in patients with completely resected stage IB to IIIA [American Joint Committee on Cancer (AJCC) 7th edition] ALK-positive non-small cell lung cancer (NSCLC) (1). A significant benefit was also seen in central nervous system DFS (CNS-DFS) [hazard ratio (HR) 0.22]. Overall survival (OS) data remains immature. These positive results from ALINA are practice-changing and have led to regulatory approvals of alectinib as an adjuvant treatment for early-stage ALK-positive NSCLC.

ALINA provides evidence to support the use of adjuvant alectinib, however, the role of chemotherapy in further improving outcomes for ALK-positive patients remains an open question. In the current trial, patients were randomised to receive either 2 years of alectinib 600 mg twice daily or four cycles of platinum-based chemotherapy. Chemotherapy was not allowed in the experimental arm which differs from other adjuvant tyrosine kinase inhibitors (TKIs) trial designs (2-4). Adjuvant platinum doublet chemotherapy is an established standard of care in the management of resected early-stage NSCLC and is associated with a 5% survival benefit (5). From a theoretical perspective, both chemotherapy and targeted therapies may be beneficial due to their distinct and potentially additive mechanisms of action. Cytotoxic chemotherapy induces non-selective neoplastic cell death by targeting mechanisms involved in the survival and proliferation of both the tumor cells and their environment. Targeted therapies, such as alectinib, are cytostatic in nature and act by blocking the division of cells harboring a specific target without inducing direct cell death. In the ADAURA trial, which evaluated 3 years of adjuvant osimertinib versus placebo in epidermal growth factor receptor (EGFR) mutation-positive patients following surgical resection, the use of adjuvant chemotherapy was balanced across both treatment groups. Considering that the trial was not designed to evaluate the optimal use of chemotherapy, the DFS benefit associated with osimertinib was observed regardless of the use of chemotherapy (hazard ratio for recurrence or death of 0.16 with chemotherapy and 0.23 without chemotherapy). In addition, there was no evidence that chemotherapy was harmful (6). There is also growing interest in combining chemotherapy with targeted therapy in advanced NSCLC. The FLAURA2 trial demonstrated an improvement in progression-free survival with the combination of chemotherapy and osimertinib compared to single agent osimertinib in the first-line EGFR-positive metastatic disease (7). Retrospective evaluation of chemotherapy in

^ ORCID: 0009-0000-7126-1150.

combination with ALK inhibitors in the metastatic setting also suggests activity and is being prospectively evaluated in the ALK PPL study (8). This potential for synergy remains to be explored.

Similarly, there is uncertainty surrounding the optimal duration of treatment with targeted adjuvant therapies in NSCLC. The ALINA investigators selected a fixed duration of 2 years for adjuvant alectinib with the goal of balancing efficacy and toxicity. The ADAURA trial evaluated 3 years of adjuvant osimertinib. Although there was a significant and clinically meaningful improvement in DFS and OS, longer follow-up has shown that both DFS and CNS-DFS curves show a steeper decline following the completion of osimertinib (2,9), This finding suggests that some patients may benefit from osimertinib treatment beyond the established 3 years of adjuvant therapy. The primary survival analysis for ALINA was conducted at median follow-up of 28 months; an increase in recurrence rates is also seen after completion of the 2-year treatment period. Prospective trials and biomarkers are needed to identify which subgroup of patients may benefit from longer treatment.

In the ALINA trial, traditional stage-based risk stratification methods showed the expected trend of increasing risk of recurrence from stage IB to IIIA. With newer technologies such as liquid biopsy, the possibility of risk stratification based on postoperative plasma sampling is emerging. In the ADAURA study, personalized molecular residual disease panels were created based on whole exome sequencing of resected tumors. Only 36% of patients had sufficient sample to produce the minimal residual disease (MRD) assay. On treatment the sensitivity of the MRD assay was 65% with a specificity of 95% for disease progression. It was noted that most patients had MRD/DFS events within 12 months of completing adjuvant osimertinib, suggesting that this tool could be helpful to determine which patient should be considered for longer duration of therapy (10). In the ALK-positive metastatic setting, circulating tumor RNA (ctRNA) and circulating tumor DNA (ctDNA) detected ALK fusions and mutations have been reported in up to 75% of patients (11,12). However, the sensitivity of assays used in the metastatic setting is not sufficient for the adjuvant ALK population. There are also challenges associated with the detection of ALK fusions by next-generation sequencing (NGS), even more so with liquid biopsy where detection may be further limited by low levels of tumor DNA (13). In the ALINA study, mandatory plasma collection was performed at baseline and periodically until disease recurrence, so further insight into the role of liquid biopsy and molecular detection of residual disease will be forthcoming.

Other ALK inhibitors are being investigated in phase III adjuvant studies including crizotinib in the ECOG-ACRIN sponsored ALCHEMIST study and ensartinib (NCT02201992, NCT05341583). The optimal timing of ALK inhibition in relation to surgery is also under investigation. In the perioperative space, ALNEO-GOIRC-01-2020, a phase II trial evaluating a perioperative strategy with alectinib in ALK-positive potentially resectable stage III NSCLC, demonstrated some signal of efficacy at its first interim analysis (major pathologic response of 39%, pathologic complete response of 17%) (14). NAUTIKA1 is an umbrella study with a treatment arm exploring 8 weeks of neoadjuvant alectinib followed by adjuvant platinum chemotherapy and 2 years of alectinib (NCT04302025). The wealth of studies in the curative intent setting will shed light on the best way to use our treatment tools.

Studies on patient preferences with respect to adjuvant treatment in NSCLC have reported different results depending on the proposed therapy. The Australasian Lung Cancer Trials Group assessed patient preferences for adjuvant chemotherapy using a time-trade-off approach to determine the minimum survival benefit considered sufficient by participants. The median survival benefit considered sufficient by at least 50% of participants was 9 months beyond hypothetical life expectancies of 3 and 5 years and an additional 5% beyond hypothetical 5-year survival rates of 50% and 65% (15). With respect to targeted therapy, Roswell Park used the time-trade-off method to evaluate adjuvant osimertinib in hypothetical trade-off scenarios related to treatment preferences. The results showed that of the 51 patients enrolled, 56% required a 12-month OS benefit and 72% required a 12-month DFS benefit for consideration therapy. The study also found that 31% opted out despite a 10% OS gain, and 33% were unwilling to accept any co-payment even with a 10-year OS benefit (16). The latter study suggests that there are multiple factors including cost of treatment, patient education and employment, and toxicities, that are considered in decision-making beyond the benefits of therapy. It is anticipated that patient preferences will be similarly influenced with adjuvant alectinib.

Health-related quality of life (HRQoL) data from ALINA suggest that most patients do not report a decrease in HRQoL with therapy. The Short Form-36 version 2 showed an improvement in most domains of HRQoL by week 12, followed by maintenance of HRQoL in all 8 domains: physical functioning, role-physical, bodily pain,

general health, vitality, social functioning, role-emotional, and mental health (17). Treatment-related adverse events of grade 3–4 occurred in 18% and 28% of patients and treatment discontinuation was reported in 5% and 13%, for alectinib and chemotherapy, respectively, consistent with the HRQoL findings. Additional safety data did not raise any new concerns and confirmed the manageable safety profile of alectinib (18). There is currently no data on long-term toxicity of ALK inhibitors in the adjuvant setting, an important consideration, as patients with ALK-positive NSCLC are typically younger at diagnosis. Encouraging data from the CROWN trial after 5 years of follow-up demonstrated that treatment discontinuation due to adverse events remained low and no new safety signals emerged from long exposure to lorlatinib (19).

The use of alectinib earlier in the treatment algorithm for patients with ALK-positive NSCLC is expected to impact the management of advanced disease. In the metastatic setting, commonly identified resistance mechanisms to alectinib include on-target ALK mutations. While the G1202R mutation is the most common in this setting, other mutations involving the ALK kinase domain have been observed (I1171 T/N/S, V1180L) (20). It is suggested that in the adjuvant setting, the selection pressure from alectinib treatment may result in the predominance of these ALK mutations. Fortunately, patients who fail a second-generation ALK TKI and develop an ALK kinase domain mutation may be more responsive to a highly potent third-generation TKI, lorlatinib (21). In ALINA, 15 patients in the alectinib arm presented with recurrence—8 patients received alectinib or brigatinib as a subsequent line of treatment and 6 patients received chemotherapy. Off-target resistance to alectinib includes ALK-independent mechanisms such as histological transformation and by-pass pathways. With the correlative studies in ALINA, characterization of resistance mechanisms may help to select the best next line therapy and provide further insight into strategies to overcome resistance.

Wu *et al.* established adjuvant alectinib as a new standard of care for patients with resectable early-stage ALK-positive NSCLC, providing renewed optimism for cure in this population. Although alectinib is already approved and implemented in practice, several questions remain, including the optimal duration of treatment and the potential role of a perioperative regimen, the added value of chemotherapy and the management of relapse on ALK inhibitor therapy in early-stage disease. Studies are needed to explore the role of tools such as ctDNA and biomarkers in addressing these issues. However, an even more critical component will be the early detection of ALK-positive NSCLC in patients who do not meet standard lung cancer screening criteria and how we will address screening in patients with a never or light smoking history.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Translational Lung Cancer Research*. The article has undergone external peer review.

Peer Review File: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-844/prf

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-844/coif). M.F.D.A. declares honoraria to self for an educational presentation from Pfizer. C.H. declares grant funding from Roche and AstraZeneca paid to institution and honaria paid to self from Abbvie, Amgen, AstraZeneca, Bayer, BMS, Janssen, Jazz, Merck, Novartis, Pfizer, Roche, and Sanofi. The authors have no other conflicts of interest to declare.

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.

References

1. Wu YL, Dziadziuszko R, Ahn JS, et al. Alectinib in Resected ALK-Positive Non-Small-Cell Lung Cancer. N

Engl J Med 2024;390:1265-76.
2. Wu YL, Tsuboi M, He J, et al. Osimertinib in Resected EGFR-Mutated Non-Small-Cell Lung Cancer. N Engl J Med 2020;383:1711-23.
3. Yue D, Xu S, Wang Q, et al. Updated Overall Survival and Exploratory Analysis From Randomized, Phase II EVAN Study of Erlotinib Versus Vinorelbine Plus Cisplatin Adjuvant Therapy in Stage IIIA Epidermal Growth Factor Receptor+ Non-Small-Cell Lung Cancer. J Clin Oncol 2022;40:3912-7.
4. Kelly K, Altorki NK, Eberhardt WE, et al. Adjuvant Erlotinib Versus Placebo in Patients With Stage IB-IIIA Non-Small-Cell Lung Cancer (RADIANT): A Randomized, Double-Blind, Phase III Trial. J Clin Oncol 2015;33:4007-14.
5. Pignon JP, Tribodet H, Scagliotti GV, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. J Clin Oncol 2008;26:3552-9.
6. Wu YL, John T, Grohe C, et al. Postoperative Chemotherapy Use and Outcomes From ADAURA: Osimertinib as Adjuvant Therapy for Resected EGFR-Mutated NSCLC. J Thorac Oncol 2022;17:423-33.
7. Planchard D, Jänne PA, Cheng Y, et al. Osimertinib with or without Chemotherapy in EGFR-Mutated Advanced NSCLC. N Engl J Med 2023;389:1935-48.
8. Lin JJ, Schoenfeld AJ, Zhu VW, et al. Efficacy of Platinum/Pemetrexed Combination Chemotherapy in ALK-Positive NSCLC Refractory to Second-Generation ALK Inhibitors. J Thorac Oncol 2020;15:258-65.
9. Herbst RS, Wu YL, John T, et al. Adjuvant Osimertinib for Resected EGFR-Mutated Stage IB-IIIA Non-Small-Cell Lung Cancer: Updated Results From the Phase III Randomized ADAURA Trial. J Clin Oncol 2023;41:1830-40.
10. John T, Grohe C, Goldman JW, et al. Molecular residual disease (MRD) analysis from the ADAURA trial of adjuvant (adj) osimertinib in patients (pts) with resected EGFR-mutated (EGFRm) stage IB–IIIA non-small cell lung cancer (NSCLC). J Clin Oncol 2024;42:8005.
11. Horn L, Whisenant JG, Wakelee H, et al. Monitoring Therapeutic Response and Resistance: Analysis of Circulating Tumor DNA in Patients With ALK+ Lung Cancer. J Thorac Oncol 2019;14:1901-11.
12. Kwon M, Ku BM, Olsen S, et al. Longitudinal monitoring by next-generation sequencing of plasma cell-free DNA in ALK rearranged NSCLC patients treated with ALK tyrosine kinase inhibitors. Cancer Med 2022;11:2944-56.
13. Kasi PM, Lee JK, Pasquina LW, et al. Circulating Tumor DNA Enables Sensitive Detection of Actionable Gene Fusions and Rearrangements Across Cancer Types. Clin Cancer Res 2024;30:836-48.
14. Leonetti A, Boni L, Gnetti L, et al. MA01.03 - Neoadjuvant Alectinib in Potentially Resectable Stage III ALK-Positive NSCLC: Interim Analysis of ALNEO-GOIRC-01-2020 Phase II Trial. J Thorac Oncol 2024;19:S52.
15. Blinman P, Hughes B, Crombie C, et al. Patients' and doctors' preferences for adjuvant chemotherapy in resected non-small-cell lung cancer: What makes it worthwhile? Eur J Cancer 2015;51:1529-37.
16. Awidi M, Mier-Hicks A, Perimbeti S, et al. Patients' Preferences for Adjuvant Osimertinib in Non-Small-Cell Lung Cancer After Complete Surgical Resection: What Makes It Worth It to Patients? Clin Lung Cancer 2024;25:509-18.
17. Nishio M, Wu YL, Barlesi F, et al. Health-related quality of life (HRQoL) results for adjuvant alectinib vs chemotherapy in patients with resected ALK+ non-small cell lung cancer (NSCLC): Data from ALINA. J Clin Oncol 2024;42:8006.
18. Horinouchi H, Solomon BJ, Wu YL, et al. OA13.04 ALINA Safety Results: Adjuvant Alectinib vs Chemotherapy in Patients with Resected ALK+ Non-Small Cell Lung Cancer (NSCLC). J Thorac Oncol 2024;19:S39.
19. Bauer T, Solomon BJ, Mazieres J, et al. MA06.08 Kinetics and Management of Adverse Events Associated with Lorlatinib after 5 Years of Follow-Up in the CROWN Study. J Thorac Oncol 2024;19:S75-S76.
20. Dagogo-Jack I, Rooney M, Lin JJ, et al. Treatment with Next-Generation ALK Inhibitors Fuels Plasma ALK Mutation Diversity. Clin Cancer Res 2019;25:6662-70.
21. Shaw AT, Solomon BJ, Besse B, et al. ALK Resistance Mutations and Efficacy of Lorlatinib in Advanced Anaplastic Lymphoma Kinase-Positive Non-Small-Cell Lung Cancer. J Clin Oncol 2019;37:1370-9.

Cite this article as: D'Amours MF, Ho C. Targeting a cure in anaplastic lymphoma kinase-positive non-small cell lung cancer. Transl Lung Cancer Res 2024;13(12):3815-3818. doi: 10.21037/tlcr-24-844