Editorial

Current opportunities and challenges in ALK-positive lung cancer

Non-small cell lung cancer (NSCLC) is a genomically defined disease commonly managed with a biomarker-driven, precision medicine treatment paradigm. As of 2023, ten distinct oncogenic driver alterations have been established in NSCLC as actionable targets, each with genotype-matched therapies approved by the US Food and Drug Administration (FDA) (1). Of these, anaplastic lymphoma kinase (*ALK*) gene rearrangements, or *ALK* fusions, were the second targetable driver discovered in lung cancer (after activating *EGFR* mutations). First reported in 2007, *ALK* fusions have since been identified in 3–5% of patients (2,3). The swift advances in the clinical development of ALK tyrosine kinase inhibitors (TKIs) that followed for patients with *ALK*-rearranged (or "ALK-positive") NSCLC have come to exemplify the opportunities, successes, and challenges of precision oncology.

Indeed, over the past 13 years, we have witnessed (I) the rapid development and FDA approval of five distinct ALK TKIs, belonging to three successive "generations" that are increasingly potent, selective, and central nervous system (CNS)-penetrant (4,5); (II) the characterization of molecular mechanisms of resistance to ALK TKIs [both on-target (e.g., *ALK* kinase domain resistance mutations) and off-target (e.g., bypass signaling activation, lineage change)] (4-8) and the design of therapeutic strategies to overcome some of these mechanisms (such as higher-generation ALK TKIs to overcome *ALK* resistance mutations) (4,5,9,10); (III) a practice shift to using next-generation ALK TKIs upfront rather than after the development of resistance and tumor relapse (11-13), (IV) the adoption of evolving diagnostics for detection of *ALK* fusions and resistance alterations, including next-generation sequencing of tissue and circulating tumor DNA (14); and (V) the evaluation of ALK-targeted therapies in early-stage cancers (15-17). These clinical advances have reflected the parallel progress in our knowledge of the fundamental biology underlying ALK-positive tumors and their evolution under targeted therapy.

In this special series of *Translational Lung Cancer Research* dedicated to ALK-positive NSCLC, our esteemed colleagues present a comprehensive up-to-date review of this field, covering not only the latest advances but also the ongoing challenges. Within the scope of ALK-positive lung cancer (14), we discuss state-of-the-art treatment approaches for patients with metastatic disease and strategies to address resistance to ALK inhibitors (18,19), as well as the management of early-stage disease (20). This has clearly been a fast-moving field. In fact, since the commencement of this series, positive results from the randomized phase III ALINA trial have been presented, demonstrating a significant disease-free survival benefit conferred by the ALK inhibitor alectinib as compared to platinum-doublet chemotherapy in the adjuvant setting among patients with surgically resected ALK-positive lung cancer, which establishes adjuvant alectinib as a new standard treatment for this patient population (15). Clinical trials to assess the role of neoadjuvant alectinib (e.g., NAUTIKA-1, ALNEO) continue (16,17). Shifting to the metastatic setting, patients with ALK-positive lung cancer have multiple therapeutic options. Recent clinical trial updates have demonstrated that upfront therapy with the third-generation ALK TKI lorlatinib yielded unprecedented progression-free survival and CNS efficacy (13), with 4th-generation ALK inhibitors [e.g., NVL-655 (21)], combination strategies (4,5), and antibody-drug conjugates (22,23) in development to target ALK TKI-resistant disease.

Through the lens of ALK-positive lung cancer, we also take a deep dive into topics broadly relevant to oncogene-addicted tumors, including: (I) the biology and targeting of brain metastases (24); (II) lineage plasticity (e.g., epithelial mesenchymal transition and histologic transformation) (25); and (III) the barriers in harnessing immune responses [i.e., lack of benefit from anti-PD(L)1 immune checkpoint inhibition] and future directions for leveraging immunotherapy (e.g., ALK-directed vaccine approaches, adoptive cell therapy, oncolytic viruses) (26). Each of these topics currently represents a major scientific and therapeutic bottleneck, relevant across oncogene-addicted lung cancers, and we anticipate that breakthroughs therein will move the needle on patient outcomes. Equally critical will be understanding the molecular underpinnings of, and strategies to target, TKI-tolerant persister cells, which lead to residual disease and, eventually, frank drug resistance and cancer relapse (27).

Finally, recognizing that partnership with patients and patient research advocates is pivotal in driving impactful research, we have invited the Scientific Committee of ALK Positive Inc.—a pioneering patient-led advocacy organization dedicated to ALK—to collaborate on the launch of this series. Here, the ALK Positive Inc. Scientific Committee offer their insights on the history behind the successful growth of this organization and the avenues by which they have modeled making tangible advances in cancer care (28). We believe that partnership with patients is essential to enable patient-focused perspective, that

patient-focused perspective adds clarity and underscores the urgency of research, and that this urgency is key to accelerating innovations.

We are grateful to all authors for their valued contributions, and to the editors for giving us the opportunity to highlight ALK-positive lung cancer through this special series. We hope that the readers of *Translational Lung Cancer Research* will find the series informative and inspiring as we collectively provide care for patients with ALK-positive lung cancer and embark on collaborative research efforts to tackle the next frontier in transforming clinical outcomes.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Translational Lung Cancer Research* for the series "ALK Positive NSCLC". The article did not undergo external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-2023-4/coif). The series "ALK-Positive Lung Cancer" was commissioned by the editorial office without any funding or sponsorship. J.J.L. and J.F.G. served as the unpaid Guest Editors of the series and J.J.L. serves as an unpaid associate Editor-in-Chief of *Translational Lung Cancer Research* from October 2023 to September 2025. J.J.L. has served as a compensated consultant for Genentech, C4 Therapeutics, Blueprint Medicines, Nuvalent, Bayer, Elevation Oncology, Novartis, Mirati Therapeutics, Takeda, AnHeart Therapeutics, CLaiM Therapeutics, Ellipses Pharma, Hyku Biosciences, Regeneron, Pfizer, Daiichi Sankyo, AstraZeneca, Merus, Bristol Myers Squibb, and Turning Point Therapeutics; and received institutional research funds from Hengrui Therapeutics, Turning Point Therapeutics, Neon Therapeutics, Relay Therapeutics, Bayer, Elevation Oncology, Roche, Linnaeus Therapeutics, Nuvalent, and Novartis. J.F.G. has served as a compensated consultant for Amgen, AstraZeneca, Mariana Therapeutics, Mirati Therapeutics, Merus Pharmaceuticals, Nuvalent, Pfizer, Novocure, AI Proteins, Novartis, Silverback Therapeutics, Sanofi, Blueprint Medicines, Bristol Myers Squibb, Genentech, Gilead Sciences, ITeos Therapeutics, Jounce Therapeutics, Karyopharm Therapeutics, Lilly/Loxo, Merck, Moderna Therapeutics, and Takeda; honorarium from Novartis, Merck, Novartis, Pfizer, and Takeda; institutional research funding from Adaptimmune, Alexo Therapeutics, AstraZeneca, Blueprint Medicines, Bristol Myers Squibb, Genentech, Jounce Therapeutics, Merck, Moderna Therapeutics, Novartis, NextPoint Therapeutics, and Palleon Pharmaceuticals; research support from Novartis, Genentech and Takeda, and has equity in AI Proteins; and has an immediate family member who has equity in and is employed by Ironwood Pharmaceuticals. 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.

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Keywords: ALK-positive lung cancer; non-small cell lung cancer (NSCLC); targeted therapy

Submitted Dec 20, 2023. Accepted for publication Jan 03, 2024. Published online Jan 22, 2024.
doi: 10.21037/tlcr-2023-4
View this article at: https://dx.doi.org/10.21037/tlcr-2023-4

Cite this article as: Lin JJ, Gainor JF. Current opportunities and challenges in ALK-positive lung cancer. Transl Lung Cancer Res 2024;13(1):1-4. doi: 10.21037/tlcr-2023-4