

TREATMENT LANDSCAPE OF ALK-POSITIVE METASTATIC NSCLC

A STAKEHOLDER INTERCHANGE REPORT

INTRODUCTION

Lung cancer is the leading cause of cancer-related deaths worldwide in men and women. In 2020, this disease was the cause of 1.8 million deaths and 18% of all cancer-related deaths.¹ Most lung cancers are classified as non–small cell lung cancer (NSCLC). Of these, *ALK* rearrangement is estimated to be responsible for about 3% of all lung cancer cases.² This rearrangement can occur in any lung cancer histology, making genetic testing crucial.

Initial diagnosis of *ALK*-positive NSCLC often occurs in younger patients.³ In 2020, cancer statistics from the Surveillance, Epidemiology, and End Results (SEER) Program showed that the median age at diagnosis for unselected patients with lung cancer was approximately 71 years.⁴ Among patients in the PROFILE 1014 (NCT01154140) and the PROFILE 1007 (NCT00932893) trials, which produced data used by the FDA to approve crizotinib, *ALK*-positive metastatic NSCLC (mNSCLC) affected a younger population (median age, 53 years [PROFILE 1014]; 50 years [PROFILE 1007]).^{5,6} Patients with *ALK*-positive NSCLC commonly report never smoking, or having a light smoking history (< 10 pack-years).⁵ Brain metastases are more common among patients with *ALK*-positive NSCLC than among those without an *ALK* mutation.⁷

AJMC® hosted a scientific interchange, entitled, “Clinical Pathways in *ALK*-positive metastatic NSCLC,” on January 26, 2023. The event was moderated by **Ryan Haumschild, PharmD, MS, MBA**, director of Pharmacy Services at Emory Healthcare and Winship Cancer Institute in Atlanta, Georgia. He was joined by faculty members **Kartik Konduri, MD**, a thoracic oncologist at Texas Oncology in Dallas, Texas; **Timothy Mok, PharmD, BCPS, BCOP**, the lead for the hematology and oncology drug evaluation strategy and outcomes team at Kaiser Permanente nationally; **Erin Schenk, MD, PhD**, a medical oncologist at UHealth Lung Cancer Clinic–Anschutz Medical Campus in Aurora, Colorado; **Conor Steuer, MD**, an associate professor of hematology and medical oncology at the Emory University School of Medicine and chair of the Lung and Aerodigestive Malignancies Working Group at Winship Cancer Institute in Atlanta, Georgia; and **Thomas Stinchcombe, MD**, a medical oncologist at Duke Cancer Institute in Durham, North Carolina.

THE INFLUENCE OF *ALK* MUTATION

The *ALK* gene encodes a transmembrane tyrosine kinase on chromosome 2.⁸ When the *ALK* gene is mutated, the molecular structure of the receptor changes, leading to increased activation of the *ALK* receptor.

This mechanism has been implicated in several cancers, including in NSCLC.⁸ This mutation prompts downstream reactions that lead to unregulated activation, cell survival, angiogenesis, and proliferation.⁸

The *ALK* receptor is distributed throughout the nervous system; it may play a significant role in neurodevelopment, and it has demonstrated a crucial role in the feeling of empathy.⁵ Brain metastases are a notable concern, they are more common among patients harboring *ALK* mutation.⁷

CURRENT TREATMENT LANDSCAPE OF *ALK*-POSITIVE mNSCLC

The treatment landscape of *ALK*-positive mNSCLC is constantly evolving. Targeted therapies are actively being developed as our understanding of the disease improves. Historically, *ALK*-positive mNSCLC was treated with chemotherapy alone and was associated with low 5-year survival rates.⁹ Local treatment, such as radiation or surgical resection, may be an option depending on the progression of the disease.⁹

National Comprehensive Cancer Center (NCCN) guidelines note that depending upon disease progression, targeted therapies are now preferred alongside chemotherapy to treat *ALK*-positive mNSCLC.^{9,10} Targeted therapy primarily focuses on mutated *ALK* (eg, the *ELM4-ALK* fusion) and suppression of the resulting production of *ALK* fusion protein.¹¹ Currently, 5 targeted therapies are available for patients with *ALK*-positive mNSCLC.

Crizotinib

In 2012, crizotinib, a first-generation tyrosine kinase inhibitor (TKI), was the first agent approved by the FDA for the treatment of locally advanced or metastatic, *ALK*-positive NSCLC.¹² In the randomized, controlled, phase 3 PROFILE 1014 trial, investigators compared crizotinib and platinum-based chemotherapy as first-line therapies for patients with *ALK*-positive mNSCLC.^{10,13,14} Compared with patients given chemotherapy, those given crizotinib showed improvement in progression-free survival (PFS) (10.9 vs 7.0 months, respectively; HR for progression or death with crizotinib, 0.45 [95% CI, 0.35-0.60]; $P < .001$), objective response rate (ORR) (74% vs 45%; $P < .001$), lung cancer symptoms, and quality of life (QOL).^{10,14}

Ceritinib

In 2017, the FDA approved ceritinib, the first-to-market second-generation TKI, after reviewing results of the ASCEND-5 (NCT01828112) trial, which

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compared ceritinib with single-agent chemotherapy in adult patients with *ALK*-rearranged NSCLC whose disease progressed following use of crizotinib and platinum-based doublet chemotherapy.¹⁵ The median PFS was notably longer among the ceritinib group (5.4 months [95% CI, 4.1-6.9 months]) than among the chemotherapy group (1.6 months [95% CI, 1.4-2.8 months]) (HR, 0.49 [95% CI, 0.36-0.67 months]; $P < .0001$). According to Dr Schenk, "Major concerns with this targeted therapy were also noted, particularly gastrointestinal toxicity and some dosing issues that were later worked out."

Alectinib

The J-ALEX (JapicCTI-132316) trial was the first head-to-head comparison of alectinib vs crizotinib.¹⁶ Patients with *ALK*-positive NSCLC who had not received an *ALK* inhibitor or had received 1 or no previous chemotherapy regimen were randomly assigned to receive alectinib or crizotinib until progression, unacceptable toxicity, withdrawal, or death occurred.¹⁶ At the second interim analysis, an independent data monitoring committee found that the primary end point of PFS was met—median PFS in the alectinib group had not been reached (95% CI, 20.3 months to not estimated) and in the crizotinib group was 10.2 months (95% CI, 8.2-12.0 months).

In 2015, alectinib was granted accelerated approval to treat patients with *ALK*-positive mNSCLC who experienced progression or who were intolerant to crizotinib.¹⁷ In the NP28761 (NCT01871805) and NP28673 (NCT01801111) trials, among patients with *ALK*-positive NSCLC who experienced progression on crizotinib, the ORRs were 38% (95% CI, 28%-49%) and 44% (95% CI, 36%-53%), respectively.

In 2017, based on results from the ALEX (NCT02075840) trial, the FDA granted regular approval to alectinib for the treatment of *ALK*-positive mNSCLC as detected using an FDA-approved test.^{10,17,18} In the ALEX trial, patients with previously untreated, advanced, *ALK*-positive NSCLC were randomly assigned to receive alectinib or crizotinib.¹⁸ The 12-month event-free survival was significantly higher among the alectinib arm than among the crizotinib arm (68.4% [95% CI, 61.0%-75.9%] vs 48.7% [95% CI, 40.4%-56.9%]; HR for disease progression or death, 0.47 [95% CI, 0.34-0.65]; $P < .001$), respectively, and median PFS was not reached.¹⁸ Final independent review facility-assessed results from the J-ALEX study demonstrated that use of alectinib produced sustained improvement in PFS (HR, 0.37; 95% CI, 0.26-0.52); the median PFS was 34.1 months for

alectinib vs 10.2 months for crizotinib.¹⁹ According to Dr Schenk, alectinib is the preferred monotherapy, and brigatinib and lorlatinib are also considered.

Brigatinib

Brigatinib, another first-line option, was approved by the FDA in 2020 based on results of the ALTA-1L (NCT02737501) trial, which compared brigatinib to crizotinib in patients with *ALK*-positive NSCLC who were refractory to crizotinib.^{10,20} Results of the phase 3 trial showed an increased median PFS in the brigatinib arm vs in the crizotinib arm (29.0 months vs 13 months, respectively); among patients with measurable lesions, the confirmed objective intracranial response rates were 78% (95% CI, 52%-94%) and 29% (95% CI, 11%-52%), respectively.²¹ Patients should be monitored for development of early-onset pulmonary symptoms (eg, interstitial lung disease/pneumonitis); however, these effects may resolve quickly with minimal intervention and dose titration over 7 days.^{20,22}

Lorlatinib

The FDA approved lorlatinib in 2021 as a first-line therapy for patients with *ALK*-positive mNSCLC based on results from the CROWN (NCT03052608) trial.^{10,23} In this randomized, multicenter, open-label, active-controlled, phase 3 trial, investigators compared lorlatinib to crizotinib in patients who had not received prior systemic therapy for *ALK*-positive locally advanced or mNSCLC.²³ The study showed improved PFS with use of lorlatinib compared with the effects of crizotinib therapy. In the lorlatinib group, 78% (95% CI, 70%-84%) of patients were alive without disease progression at 12 months compared with 39% (95% CI, 30%-48%) of patients in the crizotinib group.^{23,24}

CLINICAL PATHWAYS

Value of Clinical Pathways

A clinical pathway blends expertise from many providers. The primary goal of a clinical pathway is to produce maximum value at each practice site. Dr Konduri's institution strongly emphasizes the utility of clinical pathways; they implement a standard order set that has been thoroughly studied and approved by expert committees and task forces. This practice is especially beneficial for general oncologists who do not have the same exposure to *ALK*-positive mNSCLC as do thoracic oncologists. Dr Konduri expressed concerns about providers

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not having flexibility with treatment plans when deviation from the clinical pathway is warranted. He believes that clinical pathways at his institution provide “singularity” over a complicated management landscape.

Dr Stinchcombe’s institution does not use clinical pathways; instead, health care professionals rely on NCCN guidelines. He mentioned that it is essential to remember that each patient is unique, and, in today’s practice, patient preferences for treatments present a great hurdle to overcome. He pointed out that this patient population is very proactive in understanding the disease state and available options. He feared that rigid guidelines from clinical pathways may impede a patient’s justifiable personal inclination about treatment. He strongly emphasized that flexibility must be built into these pathways to individualize them as needed.

“Part of the discussions that I have with my patients, not only at the first visit, but [at] a lot of visits, is about quality of life and toxicities, and trying to maintain a quality of life that is livable for them in the hopes that therapies can help get them to years and years out.”

— Erin Schenk, MD, PhD

Development of Pathways

Clinical pathways may be developed via a committee that is usually comprised of experts in the particular disease state. In the case of lung cancer, the committees typically include experts in thoracic oncology and pulmonary diseases. Dr Mok has extensive experience in developing clinical pathways. At his institution, the committee includes a pharmacist from the pharmacy analyst team who subspecializes in lung cancer. The committee analyzes peer-reviewed medical literature and evaluates the costs of available therapeutic options. The members then typically choose between 1 to 3 preferred therapies. Dr Mok’s institution uses Epic Beacon, the medical oncology module of the widely used Epic Systems electronic health record (EHR) program. Epic Beacon allows providers to document and manage personalized treatment plans for oncology patients. Members of the pharmacy analyst team perform a retrospective analysis/review that considers the provider level, agents chosen, and respective patient outcomes. Their practice site is an integrated delivery network (IDN); thus, they incorporate both clinical and economic considerations in developing clinical pathways.

Drug intelligence and strategy groups forecast emerging therapies and their possible effect on current clinical pathways. At Dr Mok’s

institution, approvals for clinical pathways begin with a group of subspecialty teams followed by final approval by interregional chiefs of oncology to see if any final changes are needed. The final approved pathway is then given to the Beacon teams, who begin creating protocols for implementation into the EMR system by information technology teams. Dr Mok and colleagues design clinical pathways that may be used in about 80% of patients. Efficacy and safety are always the priority; if the targeted therapies considered are of similar effectiveness and tolerability, only then is their cost factored into the decision. Dr Mok’s institution not only reviews initial dosing when conducting the economic evaluation, but also considers dosage forms and dose reductions observed in clinical trials. Dr Stinchcombe stated that cost rarely factors into the decision-making process at his practice site.

Quality of Life

Dr Mok believes that appropriate/accurate assessment of QOL is critical. Efforts are being made at his institution to pinpoint key determinants by using QOL surveys and other patient-reported outcomes; these tools have helped his organization collect large amounts of patient feedback. He explained that technology can only help so much when it comes to assessing this conundrum, rather, he believes that it is much more beneficial to have “an engaged patient” who provides “real-time feedback.” The data are limited, but a better understanding of patient-reported outcomes and real-world evidence (RWE) would be most beneficial for integration into patient management at an aggregate level. Dr Schenk agreed that adequate QOL for each patient during treatment is the priority—consideration of the many different variables that can have an impact (eg, adverse effects [AEs], financial cost) is crucial. She states, “part of the discussions that I have with my patients, not only at the first visit, but a lot of visits, is about quality of life and toxicities, and trying to maintain a quality of life that is livable for them in the hopes that therapies can help get them to years and years out.”

Challenges

A common concern shared among the providers on this panel focused on flexibility of clinical pathways and avoiding the establishment of rigid guidelines. Dr Stinchcombe preferred to purchase clinical pathways instead of having his institution convene numerous committee meetings to develop them internally.

Dr Mok suggested that education is the biggest priority when it comes to challenges with clinical pathways. Most providers are accustomed to entering a simple order, and they have no experience in clicking through a pathway that is more labor-intensive than is a standard electronic medical or health record and that may require additional clinical pearls. These clinical pearls are built into the pathway; in teaching community physicians about treatment, specialists want to emphasize any warnings associated with a particular therapeutic agent.

Another challenge involves FDA approval of new drugs not yet included on the pathway. Some providers may be eager to prescribe

these medications to their patients, which can be an issue. Dr Schenk pointed out that when providers use a pathway, they must click through questionnaires by answering positively or negatively to help ensure that molecular markers are evaluated and that the most beneficial treatment pathway is used. This practice has its vulnerabilities, as a provider can click through the question with no hard stops. Like Dr Mok, Dr Schenk noticed an extra work burden for clinicians; there have been many rollouts of pathways at her institution, and many providers don't want to be limited to these structures or "cookie-cutter" approaches to treat patients. It is challenging to balance physician autonomy with rigid clinical pathways when it comes to these institutional decisions, which often are made by a small group.

Differences in ALK-targeted Treatments and Considerations

The management of ALK-positive mNSCLC often is not straightforward or clearly defined. Dr Stinchcombe stated that clinical data often can't help him choose a specific treatment option, because every current trial compares a particular drug with crizotinib. He added that more head-to-head trials are needed to determine a single preferred therapy for NSCLC patients with ALK mutations. Dr Stinchcombe approaches the selection of targeted therapies by discussing the 3 therapeutic choices that he most prefers to use (ie, alectinib, brigatinib, and lorlatinib) and listing all of the common AEs associated with each. He takes a patient-centered care approach to discuss the most common AEs associated with each agent to come to a consensus with the patient. Lorlatinib has the lowest hazard ratio, alectinib has long follow-up phase 3 trial data, and brigatinib has pulmonary AEs that must be considered. The severity of central nervous system disease also must be assessed, because different targeted therapies may be more appropriate depending on disease progression.

In Dr Stinchcombe's experience, many patients are now prescribed alectinib. Dr Steuer agreed, adding that crizotinib and ceritinib are no longer used as first-line therapies in most settings, largely because of hepatotoxicity (ceritinib), vision problems (crizotinib), and GI toxicity (crizotinib). He prefers to not deal with pulmonary issues, as they become a heavily involved process; for example, with use of brigatinib, the physician must reduce the dose and monitor the patient after initiating the first treatment. Alectinib is his first choice of therapy in most cases.

Dr Schenk and Dr Konduri also agreed with alectinib being their first choice when treating ALK-positive mNSCLC because of their familiarity with the treatment, the long-term data, and the hazard ratio from the phase 3 trial. They both recognized limitations related to risks for toxicities. For example, Dr Konduri encountered a patient with drug-induced hemolytic anemia secondary to alectinib, which is extremely rare. However, he considered the ease of dose reduction to be an advantage when using alectinib. Further, he noted that AEs play an immense role when considering the best targeted therapy for each patient, and the greatest hurdles associated with TKI therapy are cost and concerns about resistance.

PRIORITIES IN ALK-POSITIVE mNSCLC

Dr Steuer's top priority for ALK-positive mNSCLC is increased access to genomic testing, which is commonly available at the large academic centers with which most of the experts are affiliated. At these institutions, it is common practice to run next-generation sequencing to identify oncologic mutations for selecting targeted therapeutic agents.

Dr Steuer identified the use of incorrect and outdated testing methods as a common problem in evaluating ALK-positive mNSCLC. At his institution, clinicians do not use rigid pathways; instead, they practice as a committee by adhering to general guidelines set forth by the staff. He believes that giving patients easy access to testing and therapeutics is more critical than are issues pertaining to clinical pathways. More appropriate programs must be available to help patients who encounter any insurance problems so that they may access optimal care. Further, more colleagues from other specialties (eg, radiation-oncology, interventional pulmonology) who can assist with complications should be recruited, and relationships with colleagues who can discuss treatment options for patients who are resistant to treatment should be built.

Genomic Testing Pathway: Upfront Testing vs Reflex Testing

Dr Steuer stated that the primary testing service used at Emory Hospital is Caris. Reflex testing is his great concern; it was a more straightforward process in the past, when the staff pathologist completed all genetic testing in-house when needed. Outsourcing has its hurdles, including coverage concerns with plan sponsors (eg, insurance companies, administrators) that make reflex testing more difficult.

Most of the experts practice at prominent academic institutions, so extensive molecular testing is ordered before first-line therapy begins. Dr Schenk believes that as soon as a lung cancer diagnosis is entered into the EMR system, the record should be flagged immediately so that genomic testing is completed before systemic therapy is started. This process can help patients receive the correct therapy as soon as possible and may assist with lessening resistance in ALK-targeted treatment. She believes that if first-line therapy is initiated without genomic testing, the physician is already too late, and that a genomic testing initiative could have substantial clinical and economic benefits down the line if implemented on a national scale.

The experts have varied experience when it comes to molecular testing. In Dr Stinchcombe's experience, most patients referred to his practice already had the necessary genomic testing results; this, however, was not common among the other panelists. He admitted that his institution is a referral center, so he could be unaware of insurance challenges and other biases.

Rolling Out More Genomic Testing

Dr Mok's institution is rolling out genomic testing for all relevant disease states by developing an end-to-end user pathway, so "it's

bigger than just any drug.” The pathway includes specific criteria about when testing and other scans are necessary and should be performed. Tumor boards are also involved when uncommon mutations are encountered. Clinical pathways would be most helpful to physicians other than thoracic specialists who treat lung cancer, he noted. The goal of this process is to build a standard platform nationally, because more medical professionals than just thoracic specialists are treating lung cancer.

If the diagnosis is lung cancer, [the patient] automatically needs to go through the sequencing for targets with FDA approved therapies...If you're reminding people at the time of treatments, that's too late.

— Erin Schenk, MD, PhD

Dr Schenk stated that continuing with high-level molecular testing when the disease progresses is crucial when using targeted therapies. She thinks that, “if the diagnosis is lung cancer, [the patient] automatically needs to go through the sequencing for targets with FDA approved therapies...If you're reminding people at the time of treatments, that's too late.” At any time during the disease state, the molecular makeup of lung cancer can change, providing an opportunity to reconsider treatment options. To maximize the benefits of targeted therapy, identification of any mutation other than those noted when the patient was first diagnosed would be crucial. Increased genomic testing, she said, is essential to aid in the understanding of how *ALK* mutates.

Important Considerations

Dr Steuer said that the first-line therapeutics for *ALK*-positive mNSCLC are set, and he could not imagine that a new drug would displace any of these 3 prominent drugs. During consideration of a new first-line therapy, he said, the needle moves quickly when a new investigational agent or fourth-generation drug has excellent clinical data. He hopes that these next-generation, *ALK*-positive targeted therapies will play a role in the management of early-stage lung cancer.

Dr Mok has access to an enormous amount of data (eg, information on IDNs, claims data, EMRs) that can be analyzed to improve decision-making. He added that it can be “both a blessing and curse” to have all of these data at a physician's fingertips, as it is challenging to analyze this expansive amount of information. He stated that at his institution, the internal data often do not match up with the clinical research trial data. Despite similar patient populations used, pathways have been updated to reflect the results of internal

data. Clinical pathways at his institution include direction to open clinical trials for physicians interested in enrolling patients. He did not emphasize a need to see a big difference in PFS or response rate when considering a new therapy, especially when treating patients with early-stage disease.

At Dr Stinchcombe's institution, there is no firm algorithm for evaluating emerging clinical evidence for using targeted agents for *ALK*-positive mNSCLC. Data on investigational treatments, results of investigator-initiated trials, and publications of RWE are integrated into clinical pathways. Dr Stinchcombe's team tries to review and discuss the literature as a group. He stated that it is easier to feel confident prescribing a new drug after it has been through phase 3 trials and that RWE is important to consider after a new drug hits the market. He also noted that RWE reveals a low compliance rate with molecular testing across the country; hopefully, this will be remedied in the future.

FINAL THOUGHTS

Clinical pathways are helpful for physicians treating mNSCLC who are not subspecialized in thoracic oncology. Dr Steuer said that there is no direct benefit to these pathways in a large academic center, because most providers treating these patients are subspecialists in thoracic oncology. When adding clinical pathways, he stated, the additional work can be a nuisance to some of these providers. He noted that clinical pathways may have a larger role in community oncology. Further, implementation of clinical pathways may be complemented with continuing medical education, which can help provide physicians with background and understanding of the full scope of each treatment choice being considered. Keeping up with the latest research is complicated for someone treating all cancer types, so the design of clinical pathways is incredibly impactful for these providers and their patients.

Dr Schenk agreed that these pathways are significant for physicians who do not subspecialize in thoracic oncology. Having a team that includes a social worker and financial manager to help explain health care costs to patients for any potential financial burden would immensely benefit both the patient and provider. Further, consideration of financial toxicity is essential when preserving a patient's QOL. In addition, imperative points to consider include the required frequency of administering toxic therapy and the ultimate goals of treatment. She emphasized testing that is complementary and overlapping, and is needed to identify patients with an *ALK* fusion event, because such findings can strongly impact expectations for survival and outcome.

For Dr Mok, numerous issues exist regarding the creation and maintenance of clinical pathways. First- and second-line therapeutic options now include precise, targeted agents. There now are many opportunities to optimize therapy by guiding physicians to the best literature and considering use of immunotherapy alone and with chemotherapy. From his perspective, a retrospective review of clinical pathways is needed to improve the user experience, the pathways

themselves, and, most importantly, patient outcomes. He worried about the willingness of physicians to use the system in the first place, as he stated, “Without the initial buy-in of physicians utilizing the clinical pathway, it is going to be difficult for us to collect the data.”

Finally, Dr Stinchcombe added that the pathway would be more beneficial if the pathway developers included safety mechanisms (eg, when to order electrocardiogram to help minimize the risk of QT prolongation) and if the pathways could highlight potential drug interactions. Such safety mechanisms are more important to him than would be a tool to help with treatment selection. •

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