Review Article

Advancements of ALK inhibition of non-small cell lung cancer: a literature review

Victor Zia[1], Csongor György Lengyel[2], Carla Chizuru Tajima[3]^, Ramon Andrade de Mello[1,4,5,6,7]^

[1]Post-graduation Program in Translational Medicine, University Federal of São Paulo, São Paulo, Brazil; [2]Department of Head and Neck Surgery, National Institute of Oncology Hungary, Budapest, Hungary; [3]A BP – Hospital Beneficência Portuguesa de São Paulo, São Paulo, Brazil; [4]Post-Graduation Programme in Medicine, Nine of July University (UNINOVE), São Paulo, Brazil; [5]Section of Medical Oncology, Brazilian Society of Cancerology (SBCANCER), Salvador, Brazil; [6]Department of Oncology, University of Oxford, Oxford, UK; [7]Oxford Cancer Centre, Oxford University Hospitals NHS Foundation Trust, Oxford, UK

Contributions: (I) Conception and design: All authors; (II) Administrative support: All authors; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Prof. Ramon Andrade de Mello, MD, MBA, PhD, FACP. Post-graduation Program in Medicine, Precision Oncology & Health Economics Research Group (OncoPRECH), Faculty of Medicine, Nine of July University (UNINOVE), Rua Vergueiro, 235, 01533-010, São Paulo, Brazil. Email: ramondemello@gmail.com.

Background and Objective: The therapeutic landscape for non-small cell lung cancer (NSCLC) has evolved considerably in the last few years. The targeted drugs and molecular diagnostics have been developed together at a fast pace. This narrative review explores the evolution of anaplastic lymphoma kinase (ALK) targeting therapies from discovering the ALK protein, molecular tests, present clinical trial data and future perspectives. Since the body of evidence on lung cancer is growing daily, most oncologists need time to implement data in their daily practice.

Methods: We developed a narrative review to provide up-to-date help in the clinical decision-making of ALK-altered NSCLC patients. In 2022, the authors reviewed PubMed's published pivotal randomized Phase 3 trial results.

Key Content and Findings: The development of ALK inhibitors was a revolution that is still ongoing; second and third-generation ALK inhibitors provided more than 30 months of progression-free survival (PFS) and impressive "brain-control". Brigatinib provided a survival benefit for patients with baseline brain metastases (HR 0.43, 95% CI: 0.21–0.89), and Lorlatinib demonstrated intracranial response rates of 82%, with 71% of complete intracranial responses. Personalized medicine is the new paradigm, from performing broad genetic panels for diagnosis to individual targeted therapy or combinations of different targeted agents.

Conclusions: In the future, performing broad molecular panels should be the standard of care in the front line and after each progression to detect arising resistance mechanisms. Longer PFS will substantially convert a deadly condition into an almost chronic disease in the following decades. Treatment sequencing will be the cornerstone for patient survival, and liquid biopsies may replace tissue biopsies.

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

Submitted Aug 26, 2022. Accepted for publication Jun 19, 2023. Published online Jul 04, 2023.
doi: 10.21037/tlcr-22-619
View this article at: https://dx.doi.org/10.21037/tlcr-22-619

^ ORCID: Carla Chizuru Tajima, 0000-0002-9260-2505; Ramon Andrade de Mello, 0000-0002-9640-4573.

Introduction

Lung cancer is the leading cause of death worldwide. Recent data from Globocan demonstrated that lung cancer stood first in mortality in 2020, accounting for 1,796,144 deaths, followed by colorectum, liver and stomach (1). Non-small cell lung cancer (NSCLC) accounts for 85% of lung cases and usually is diagnosed in an advanced stage (2).

The therapeutic arsenal for the treatment of advanced lung cancer has evolved significantly in recent years; in addition to previous cytotoxic chemotherapy, strategies have been shown to inhibit epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK), changing the natural course of the disease (2).

The different combinations of platinum-based therapies (platinum-doublet) were considered standard when treating advanced NSCLC; all of them proved to be equivalent when compared with each other in a clinical trial published in 2002 by Eastern Cooperative Oncology Group (ECOG) (3). At that time, the standard of care was established with no need to refine the patient selection based on clinical characteristics other than performance status (3). Chemotherapy was almost the only treatment that could be used.

Despite the high heterogeneity of NSCLC, the characterization of driver mutations allows for treating each patient with a personalized approach (3). The use of next-generation sequencing (Foundation One, Oncomine, Therascreen, Guardant360 and others) is also expanding, and these advancements have led to the rapid evolvement of novel target-selected therapies (4).

Objectives

The evidence in lung cancer *ALK* translocated lung cancer is growing daily, and oncologists must identify the best approach for each patient. A data review is important to compare the ALK inhibitors in light of new studies. This review aims to help clinicians to choose the best therapy for their clinical practice. We present this article in accordance with the Narrative Review reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-619/rc).

Methods

Comprehensive research was performed in 2022, and pivotal, randomized, phase 3 trials were selected and analyzed by all authors. PubMed was the search engine for this narrative review (*Table 1*). All authors joined with different levels of responsibilities according to their expertise. *Table 1* describes the search strategy.

Molecular testing

Adenocarcinoma of the lung (LUAD) is the most common histology of NSCLC; common therapeutical targets (EGFR, ALK, PD-L1, NTRK, BRAF) of LUAD involve alterations in the epidermal growth factor receptor (*EGFR*) and *ALK* genes (5). The most prevalent activating mutations in *EGFR* are in exons 19 and 21 (5). The prevalence of *EGFR*-mutation in NSCLC is 23.9% for all subtypes of NSCLC in the US (6). Approximately 5% of NSCLC patients have *ALK* rearrangement, also known as "echinoderm microtubule-associated protein-like" (*EML4-ALK*) fusion, which activates the cell signaling cascade for cell proliferation (6).

Other rare driver alterations are observed in the proto-oncogene 1 (*ROS1*) rearrangements, accounting for 1% to 2% of LUAD patients (7). B-Raf (*BRAF*) proto-oncogene mutations, presented most as *BRAF V600E* mutation, are observed in 2–4% of LUAD patients (7).

There are several approved tests identifying mutations for NSCLC (FoundationOne, Guardian360, Ventana and others); current guidelines such as the European Society for Medical Oncology and American Society for Clinical Oncology (ASCO) advocate comprehensive molecular tests for most scenarios of advanced NSCLC (*Table 2*). It is also necessary to differentiate Complementary versus Companion diagnostics (8). Complementary has existed for decades, and Companion appears for the first time in a complementary on US Food and Drug Administration (FDA) guidance in 2003. Currently, the term "complementary" is more related to a therapeutic area, and "companion" is related to specific drugs (8). *Table 2* describes Companion FDA-approved tests for NSCLC.

The biomarkers recommended to be tested in the frontline by ASCO guidelines are *EGFR*, *KRAS*, *ALK*, *ROS-1*, *BRAF*, *RET*, *MET*, *NTRK* and *HER2*, and programmed death-ligand 1 (PD-L1), the last one to select checkpoint inhibitors for advanced NSCLC patients (11,12). *Figure 1* describes the molecular testing guidelines for evaluating NSCLC patients for EGFR or ALK-directed therapy recommended by the College of American Pathologists (CAP), the International Association for the Study of Lung Cancer (IASLC), the Association for Molecular Pathology (AMP) and ASCO.

Table 1 Search strategy table

Items	Specification
Date of search	01 May 2022
Databases and other sources searched	PubMed
Search terms used	Lung Cancer; Non-small Cell Lung Cancer; ALK therapy; Alectinib; Brigatinib; Ceritinib; Crizotinib; Entrectinib; Ensartinib; Lorlatinib
Timeframe	01 February, 2022 – 01 May, 2022
Inclusion and exclusion criteria	Inclusion criteria: phase III randomized controlled trials; English language. Exclusion criteria: other criteria which do not fulfill inclusion criteria
Selection process	The selection has been conducted independently by the authors Victor Zia and Csongor György Lengyel. The authors individually discussed all the discrepancies, and Prof. Ramon Andrade de Mello served as the scientific reviewer

ALK, anaplastic lymphoma kinase.

For different techniques in molecular testing, the amount of tissue samples available can be a central issue. When choosing a biopsy site for molecular screening for leading mutations, biopsy of the primary tumor is most often used as a surrogate for metastatic lesions (13). A suitable tissue sample (adequate cellularity and preservation) is essential for accurate diagnosis. Biopsies of metastatic bone lesions are not suggested because decalcifying agents make samples deficient for molecular testing (6).

Liquid biopsy (LB)

In the past years, *EGFR* testing was recommended only at the frontline with circulating tumor DNA (ctDNA) therapy when the amount of tissue was insufficient or after acquired resistance to 1st/2nd generation EGFR tyrosine kinase inhibitors (TKIs) to detect *EGFR* exon 20 p.T790M mutation (14). With the therapeutic arsenal's evolution, it has become essential to have broader coverage of molecular targets instead of testing a single gene in the frontline or after progression. NGS technology offers broad coverage and is recommended by most guidelines instead of gene-by-gene PCR (15-19).

LB is receiving more indications in solid tumors and is following the advances in clinical practice. It has significant potential advantages over tissue biopsies, of which the less invasive approach is considered the most attractive (15,16). The first central question for physicians is to decide to follow "*plasma first*" versus "*tissue first*" approach. The use of a tumor tissue sample is still considered the "gold standard" for molecular diagnostics and is always recommended in the frontline; unfortunately, only 18% of NSCLC patients have proper tissue for adequate genotyping and liquid biopsy appears as a complementary tool (15,16).

The sensitivity of detecting an *ALK* rearrangement using LB-based NGS may be better by focusing more on well-controlled preanalytical steps, adequate amount of plasma and shortening the delay between sampling and centrifugation (20). The gold standard of LB-based *ALK* testing still needs to be set and improved. Some authors advise using exosomal RNA (21), while others advocate the usage of circulating tumor cells (CTCs) for the detection of EML4-ALK rearrangement (22). By examining two patients with EML4-ALK rearrangement during ALK-inhibitor treatment with serial sampling, *EML4-ALK* rearrangement was detectable in circulating tumor cells (CTCs) (22). Authors also have observed a potential inverse association between the presence of biomarkers and therapeutic responses. Sometimes the availability and accessibility of the tumor can be limited and, when a new tissue biopsy is required, it could be a real challenge (23,24). Disadvantages for tissue specimens are their longer turn-around time and serial assessment is near impossible due to invasiveness (15,23). Some advantages of liquid biopsies are overcoming tissue heterogeneity, evaluating minimal residual disease and tumor resistance and monitoring the treatment's efficacy with serial testing (25).

The discovery of a new protein

The new pathway in the treatment of NSCLC was really identified in several ascent steps, from *in vitro* with cell lines to a patient with NSCLC; the scientist *Manabu Soda* played the central role in this scientific advance. In 1994, the ALK

Table 2 FDA approved tests for advanced NSCLC (8-10)

FDA-approved device	Manufacturer	Platform	Drug
Therascreen EGFR RGQ PCR kit	Qiagen	PCR	Iressa (gefitinib)
			Gilotrif (afatinib)
			Vizimpro (dacomitinib)
FoundationOne CDX	Foundation medicine	NGS	Tagrisso (osimertinib)
			Alecensa (crizotinib)
			Alunbrig (brigatinib)
			Xalkori (crizotinib)
			Zykadia (ceritinib)
			Tafinlar (dabrafenib) in combination with Mekinist (trametinib)
Cobas EGFR Mutation test V2	Roche	PCR	Tarceva (erlotinib)
			Tagrisso (osimertinib)
			Iressa (gefitinib)
			Gilotrif (afatinib)
			Vizimpro (dacomitinib)
PD-L1 IHC 22C3	Agilent technologies	IHC	Keytruda (pembrolizumab)
			Libtayo (cemiplimab-rwlc)
PD-L1 IHC 28-8	Dako	IHC	Opdivo (nivolumab) Yervoy (ipilimumab)
PD-L1 (SP263) Ventana	Ventana	IHC	Imfinzi (durvalumab)
			Keytruda (pembrolizumab)
PD-L1 (SP142)	Ventana	IHC	Tecentriq (atezolizumab)
Ventana ALK	Roche/Ventana Medical Systems	IHC	Zykadia (ceritinib)
			Xalkori (crizotinib)
			Alecensa (crizotinib)
			Lorbrena (lorlatinib)
Guardant360 CDx	Guardant Health, Inc.	NGS	Tagrisso (osimertinib)
			Rybrevant (amivantamab)
			Lumakras (sotorasib)
Vysis ALK Break Apart Fish Probe kit	Abbott	FISH	Xalkori (crizotinib)
			Alunbrig (brigatinib)
O/RDx-LCCA	Pillar Biosciences, Inc.	NGS	Iressa (gefitinib)
			Gilotrif (afatinib)
			Tarceva (erlotinib)
			Vizimpro (dacomitinib)
Oncomine™ Dx Target Test	Thermo Fisher	NGS	Tafinlar (dabrafenib) in combination with Mekinist (trametinib)
			Iressa (gefitinib)
			Xalkori (crizotinib)
			Gavreto (pralsetinib)
			Exkivity (mobocertinib)
			Rybrevant (amivantamab)

AJCC, American Joint Committee on Cancer; EGFR, epidermal growth factor receptor; PCR, polymerase chain reaction; FISH, fluorescence in situ hybridization; NGS, next-generation sequence; IHC, immunohistochemistry; ALK, anaplastic lymphoma kinase; NSCLC, non-small cell lung cancer; O/RDx-LCCA, ONCO/Reveal Dx Lung Cancer Assay; PD-L1, programmed death-ligand 1; RGQ, Rotor-Gene Q real-time PCR instrument.

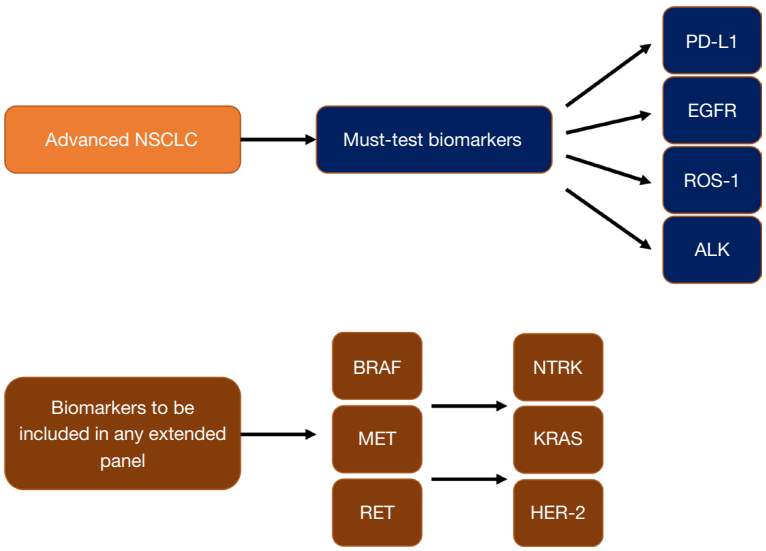

Figure 1 CAP/IASLC/AMP and ASCO recommendations for biomarkers testing. NSCLC, non-small cell lung cancer; PD-L1, programmed death-ligand 1; EGFR, epidermal growth factor receptor; ROS-1, ROS Proto-Oncogene 1; ALK, anaplastic lymphoma kinase; BRAF, B-Raf Proto-Oncogene; MET, MET Proto-Oncogene; RET, RET proto-oncogene; NTRK, neurotrophic tyrosine kinase receptor; KRAS, Kirsten rat sarcoma virus oncogene; HER-2, Erb-B2 Receptor Tyrosine Kinase 2 gene; CAP, College of American Pathologists; IASLC, International Association for the Study of Lung Cancer; AMP, Association for Molecular Pathology; ASCO, American Society of Clinical Oncology.

was found in anaplastic large cell lymphoma (ALCL) cell lines (26). In 2007, Soda *et al.* discovered the "echinoderm microtubule-associated protein 4" in a patient with NSCLC. At that time, science was still not aware of ALK receptors in NSCLC. At the chromosomal level, the *ALK-EML4* gene fusion (the main fusion in *ALK* gene) causes an inversion in the short arm of chromosome 2 that juxtaposes the N-terminus of the *EML4* gene promoter and the kinase domain of the ALK gene (27). *Figure 2* details the formation of the *EML4-ALK* fusion.

ALK was first identified as a fusion partner of nucleophosmin (NPM) in anaplastic large-cell lymphoma, with a t(2;5) chromosome rearrangement. The *EML4-ALK* (resulting in the fusion of the entire intracellular kinase domain of ALK to the corresponding partner) and the kinase activity of NPM-ALK were shown to be essential for the proliferation of *ALK*-positive cells (27) (to simplify, we considered ALK-positive as the same as *EML4-ALK* translocation, the most common ALK translocation) (27).

The *EML4* fusion partner mediates ligand-independent activation of *ALK* and constitutive kinase activity, leading to the proliferation and survival of the cancer cells responsible for 3–7% of NSCLC (28). There are several fusion partners identified for NSCLC (*Figure 3*). It is well-known that fusion variants have different prognoses, and *EML4-ALK* V3 is associated with a better prognosis (29).

ALK translocations and oncogenesis

ALK is a member of the insulin receptor tyrosine kinase family (RTK). Members of this family include EGF receptor, HER/2 neu, insulin, PDGF, with IGF-1 receptors triggering neoplastic transformation (30,31). The *ALK* was associated with (2;5)(p23; q35) chromosome translocation in CD30 positive Ki-1 lymphoma or ALCL (30). This translocation has also been associated with Hodgkin lymphoma (31). *ALK* mutations can develop various neoplasms, such as rhabdomyosarcoma, neuroblastoma, inflammatory myofibroblastic pseudotumor, and non-small cell lung cancer (30).

The *nucleophosmin (NPM)* gene encodes the nucleophosmin protein, which has been postulated that it provides positive feedback to cell growth (32,33). The fusion gene named *NPM-ALK* encodes a chimeric receptor tyrosine kinase (RTK), leading to the activation of phospholipase C-y (PLC-y). The consequence of this activation is the growth factor-independent proliferation of lymphocytes (32).

Another oncogenic mechanism is the fusion of ALK with *NPM*, leading indirectly to hyperphosphorylation

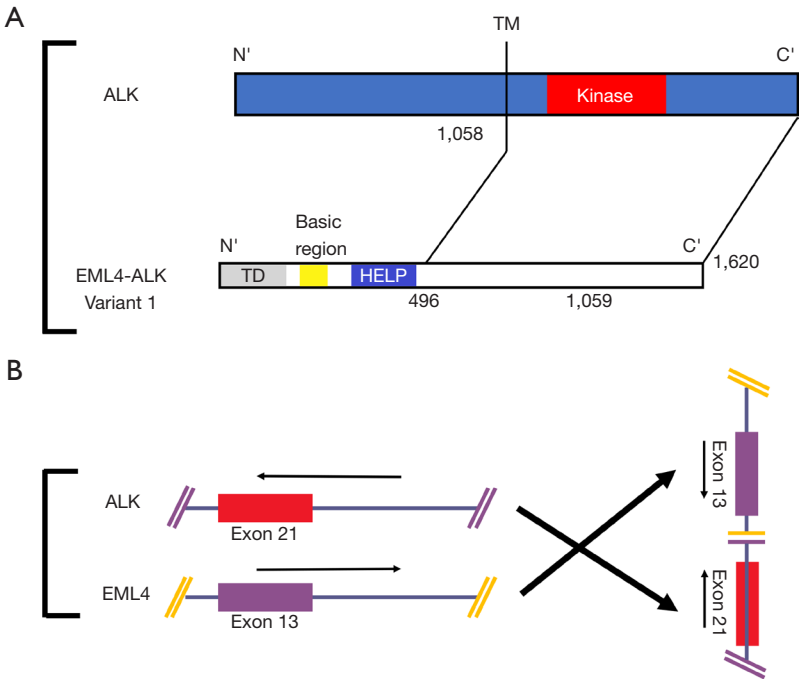

Figure 2 Gene fusion between EML4-ALK. (A) Fusion of the N-terminal portion of EML4 to the intracellular C-terminal region of ALK. (B) Both the ALK gene and EML4 with opposite orientations. Basic region: responsible for microtubule association. ALK, anaplastic lymphoma kinase; TM, transmembrane domain; TD, trimerisation domain responsible for self-association; HELP, hydrophobic echinoderm microtubule-associated protein-like protein domain.

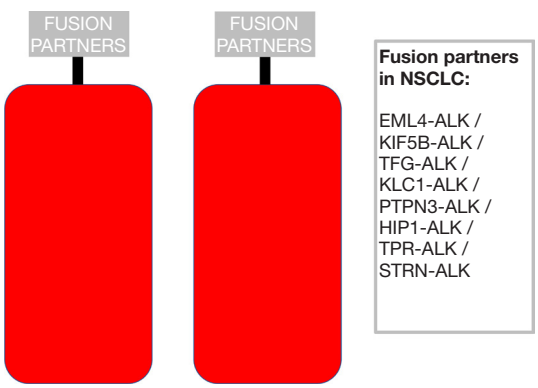

Figure 3 ALK fusion partners in NSCLC. The kinase domain of ALK (red) is fused to several protein fusion partners (grey). ALK, anaplastic lymphoma kinase; NSCLC, non-small lung cell cancer.

of p80 and resulting in downstream effects on *RAS* and *EGFR* pathways (32). Several other mechanisms have been described as the activation of JUN proteins (cJun, JunB and JunD). Jun proteins are members of the activated protein 1 (AP-1) transcription factor complex and are involved in several mitotic processes, such as the activation of Cyclin proteins and the inhibition of p53, $p21^{Cip1}$ and $p16^{Ink4}$ (30).

NPM-ALK also acts through STAT (signal transducer and activator of transcription), acting directly in the mechanism of carcinogenesis and with phosphorylation of $p60^{c\text{-}src}$. The non-muscle tropomyosin encoded by the *TPM3-ALK* mutation has been shown to be fused to *NTRK1* tropomyosin in some cancers. Another *ALK* translocation results in a fusion between *ALK* and the *ATIC* gene, which encodes an enzyme that catalyzes the pathological activation of *ALK* (30).

The *EML4-ALK* fusion protein plays an essential role in the malignant transformation of lung parenchyma (30). This fusion arises from inv (2) (p21p23), which leads to the fusion of the *EML4* gene with the *ALK* gene. Intracellular kinase activity is thought to be responsible for the transforming activity of the fusion protein (30).

Clinical development of ALK inhibitors

The *EML4-ALK* fusion gene was first identified in NSCLC (27,34). Following this important discovery, crizotinib was developed as the first ALK inhibitor (27,34). The

development of crizotinib was followed by the development of several other ALK inhibitors, as follows:

(I) Crizotinib is an oral TKI, developed originally as and inhibitor of c-MET. The activity of Crizotinib against ALK was observed in the phase I dose-escalation PROFILE 1001 study (35). Two phase III trials (PROFILE 1014 and PROFILE 1007) confirmed high activity against the standard of care chemotherapy regimens in the first and second-line regimens, respectively (35). The first-line PROFILE 1014 study demonstrated significantly superior PFS (as the primary endpoint of the trial) against chemotherapy (10.9 versus 7 months—HR 0.45; 95% CI: 0.35–0.60), with overall response rate (ORR) of 74% in the crizotinib arm *vs.* 45% in the standard chemotherapy (P<0.001) arm (36,37). ROS-1 is another TK receptor detected in NSCLC, considered to be involved in cancer cell proliferation and prolonged survival. Crizotinib also has proved efficacy against ROS-1 receptor and received FDA approval in 2016 (35).

(II) Brigatinib is a second-generation ALK inhibitor with an inhibitory profile against 17 resistance mutations, including the most common G1202R and L1196M mutations (35). This ALK inhibitor has demonstrated 12-fold higher *in vitro* potency than Crizotinib and received FDA approval for first-line treatment of *ALK*-positive NSCLC in May 2020, based on the results of the PHASE III ALTA-1 trial (35). The phase III randomized 'ALK in Lung Cancer Trial of brigatinib in 1st Line' (ALTA-1L) trial enrolled inhibitor-naïve advanced NSCLC patients and demonstrated superior PFS and response rate against Crizotinib. The final analysis of the trial (at a median follow-up of 40.4 months for Brigatinib, enrolling a total of 275 patients) demonstrated the 3-year PFS of 24.0 months for Brigatinib versus 11.1 months for Crizotinib (HR 0.48, 95% CI: 0.35–0.66) (38). A post hoc analysis suggested a survival benefit for patients with baseline brain metastases (HR 0.43, 95% CI: 0.21–0.89). Brigatinib showed excellent efficacy beyond *EML4-ALK* variant and TP53 mutation (38).

(III) Alectinib is another potent second-generation ALK inhibitor and "Rearranged During Transfection" (RET) inhibitor. The two main first-line trials are J-ALEX and ALEX. The phase III Japanese J-ALEX study enrolled 207 patients to receive Alectinib 300 mg twice daily or Crizotinib 250 mg twice daily (35). At 42.2 m follow-up, the PFS as the primary endpoint was 34.1 m for Alectinib versus 10.2 m (HR 0.37) for Crizotinib (39). The ALEX phase III trial enrolled 303 treatment naïve patients with metastatic NSCLC and Caucasian origin. Patients were randomized for Alectinib or Crizotinib, and the median PFS was more prolonged than with Alectinib (34.8 *vs.* 10.9 m, HR 0.50; 95% CI: 0.36–0.70). The ORR was 82.9% with Alectinib and 75.5% with Crizotinib (P=0.09) (40). Although there was a difference in Alectinib dose between the two studies (the ALEX study used 1,200 mg daily and J-ALEX 600 mg daily), in November 2017, the FDA-approved alectinib for first-line treatment of ALK-positive NSCLC. The results of the ALESIA trial, which included only Asian patients, also supported alectinib over crizotinib as a first-line treatment option for *ALK*-positive NSCLC (35).

(IV) Ceritinib is known as a second-generation ALK inhibitor and received FDA approval for the first time in 2014 for patients who progressed after Crizotinib (35). Ceritinib received its first-line approval in 2017. The first-line ASCEND-4 trial randomized *ALK*-positive NSCLC patients to receive Ceritinib or platinum base chemotherapy until disease progression or unacceptable toxicity. The mPFS achieved was 16.6 m with Ceritinib versus 8.1 m for chemotherapy (HR 0.55; 95% CI: 0.42–0.73), with overall response rates of 73% for Ceritinib compared to 27% observed in the chemotherapy arm (41). Contrasting with other second and third-generation TKIs, Ceritinib was compared to a chemotherapy arm, not to Crizotinib; however, some metanalyses proved the benefit of Ceritinib.

(V) Lorlatinib, considered a third-generation TKI targeting ALK and ROS-1, has demonstrated a 62-fold increased activity compared to Crizotinib. Lorlatinib has been designed to provide high central nervous system (CNS) penetration and coverage of resistance mutations to Crizotinib and next-generation TKIs (35). Based on results of phase II trials, Lorlatinib received accelerated approval for patients who progressed on Crizotinib and at least one another TKI (35). The global phase III,

first line, randomized trial (CROWN trial) was the pivotal study for Lorlatinib, leading to its regulatory approval (42). At the data cutoff on September 20, 2021, the median duration follow-up for PFS was 36.7 months for Lorlatinib and 29.3 months for Crizotinib (43). PFS by BIRC was NR (95% CI: NR–NR) for Lorlatinib and 9.3 months for Crizotinib (95% CI: 7.6–11.1), with HR 0.27; 95% CI: 0.18–0.39) (43). The results for intracranial response and intracranial progression were impressive and previously unseen. IC-TTP HR was 0.10 (95% CI: 0.04–0.27). The confirmed complete response was 60% for Lorlatinib and 9.4% for Crizotinib (43).

(VI) Ensartinib is another second-generation TKI developed for its high CNS efficacy (35). This molecule has activity against not only *ALK* variants (F1174, C1156Y, L1196M, S1206R, T1151 and G1202R mutants), but also against *MET*, *Axl*, *ABL*, *EPHA2*, *LTK*, *ROS-1* and *SLK* (35). The phase III trial (Exalt3) is an open-label, multicenter, randomized trial that randomized (1:1) 290 patients to receive Ensartinib or Crizotinib (44). The primary endpoint was systemic PFS. In the ITT (intention to treat) population, the PFS was 25.8 m for Ensartinib versus 12.7 for Crizotinib (HR 0.51; CI: 0.35–0.72, P<0.001) with a follow-up of 23.8 for Ensartinib and 20.2 for Crizotinib (44). The intracranial response rate was 63.6% with Ensartinib *vs.* 21.1% with Crizotinib for patients with measurable brain metastasis. The frequency of dose reductions and serious adverse events were similar between the two groups. No new safety signals were reported (44).

(VII) Entrectinib is a potent oral inhibitor of TRKA, TRKB, TRKC, ROS-1 and ALK. This novel ALK TKI was evaluated in two phase I/II basket trials, with only 27 patients with *ALK*-rearranged tumors (35). Among 19 patients pretreated, no response was recorded. In another 7 TKI-naïve patients, the ORR was 57% (95% CI: 25–84%), and responses were observed in NSCLC, renal carcinoma and colorectal cancer (45,46).

Discussion

The last decade established a landmark in the treatment of *ALK*-positive NSCLC as the most relevant guidelines propose first-line target therapy instead of chemotherapy (10). More comparative data must be available on different ALK inhibitors from a pharmacoeconomic perspective, highlighting which inhibitor is more cost-effective in which clinical scenario.

The advent of the new generation ALK TKIs has changed the course of brain metastases. The 40.4 months follow-up of the ALTA-1L trial demonstrated notable intracranial PFS difference among the Brigatinib treated (24.0 months median) patients versus the Crizotinib treated (5.5 months median) control arm (HR 0.29; 95% CI: 0.17–0.51; P<0.0001) (42). The response rate of first line Brigatinib was 78% versus 26% for Crizotinib. Lorlatinib is considered a third-generation TKI and has high CNS penetration. In the Phase III trial (CROWN study), Lorlatinib achieved 71% CNS complete responses, an outcome never seen before with any other new-generation TKI. Lorlatinib demonstrated an intracranial response rate of 82% among patients with measurable brain metastasis (42).

New generation ALK TKIs have different toxicity profiles (38,40,42). Lorlatinib showed 72% of grade 3 or greater side effects in the pivotal CROWN trial; in comparison, Brigatinib in the ALTA-1L trial had 73% and Alectinib in the ALEX study 50%. Contrasting with mentioned TKIs above, Lorlatinib showed 34% of Peripheral neuropathy (all grades) and 21% of cognitive effects (all grades). Cognitive effects are represented by memory impairment, disturbance in attention, confusion, amnesia, cognitive disorder, and delirium (42). Brigatinib is also considered a safe and effective therapy but has slight superior rates of pneumonitis of grade 3 or 4 (3%) compared with other TKIs (38,40,42). Ceritinib also has some specific patterns of side effects like all grades of diarrhea (85%), nausea (69%), vomiting (66%), increased ALT (60%) and AST (53%) (41).

Brigatinib, Alectinib and Lorlatinib have demonstrated high brain penetration, with the highest intracranial response rates (38,40,42). The development of new ALK-inhibitors has changed the natural course of NSCLC with brain metastases and improved the patients' quality of life. It is well accepted to use second or third-generation ALK inhibitors as a first-line therapy when a patient has limited volume brain metastasis due to high penetration of these drugs through the blood-brain barrier (47). This strategy is based on the very low rate of CNS progression for the second-generation ALK TKIs per year (<10%), which is similar to *EGFR*-positive disease in the well-known Flaura trial when Osimertinib proved to offer high cerebral control

only for asymptomatic lesions; real-world evidence suggests the same benefit for symptomatic lesions (48,49).

Another key point is the treatment sequencing when managing metastatic NSCLC. The statement that the more potent drug should be positioned in the first line is well established for *EGFR* positive NSCLC, in which Osimertinib has been proved superior to the previous generation EGFR TKI when used in sequencing (48). For ALK therapy, the argument for using next-generation TKI in at first line instead of Crizotinib, is based on intracranial disease control and more significant PFS when sequencing Crizotinib and new-generation TKIs (38,40). Brain control is all the more important as most patients with *ALK*-positive lung cancer are young.

Conclusions

In addition to the many recent achievements in the development of ALK inhibitors, central, open questions remain in clinical decision-making. When choosing an ALK inhibitor, physicians must balance clinical benefit (PFS, OS) and toxicity, remembering that access to new target therapies is not equal worldwide. The treatment sequencing is also an important question, but data for third-generation ALK inhibitor Lorlatinib is not entirely mature. If future data show that first-line Lorlatinib PFS would be longer than the sequence of a second generation followed third-generation TKI, Lorlatinib will probably be positioned in frontline. The remaining question will be the coverage of resistance mutations for third generation TKI.

Future perspectives

The future of treating *ALK*-positive NSCLC may be to understand and prevent the development of resistance to next-generation ALK inhibitors by a co-targeting approach, with liquid biopsies helping to identify newly acquired emerging resistance mechanisms. Performing broad molecular panels would be the standard of care in the frontline and after each progression. Treatment sequencing will be the cornerstone for patient survival and liquid biopsies would replace tissue biopsies. Global access to new cancer therapies should improve in the following years to share the benefit of new cancer treatments with the global population (find at *Table 3* the ongoing clinical trials for NSCLC).

Table 3 Summary of current ongoing clinical trials in ALK-fusion-positive NSCLC

No.	Title	Conditions	Interventions
1	A Study of Brigatinib to Treat Adults With Anaplastic Lymphoma Kinase (ALK) Positive Metastatic Non-Small Cell Lung Cancer (NSCLC)	• Carcinoma, non-small cell lung • Anaplastic lymphoma kinase	• Other: no intervention
2	Lorlatinib After Failure of First-line Second-generation ALK Kinase Inhibitor in Patients With Advanced ALK-positive Nonsmall Cell Lung Cancer	• Non-small cell lung cancer metastatic	• Drug: Lorlatinib
3	Alectinib in Neo-adjuvant Treatment of Stage III NSCLC	• Non-small cell lung cancer	• Drug: Alectinib
4	Lorlatinib Continuation Study	• Non-small cell lung cancer • NSCLC	• Drug: Lorlatinib
5	A Study of Brigatinib Compared to Alectinib in Adults With Non-Small-Cell Lung Cancer	• ALK$^+$ advanced NSCLC	• Drug: Brigatinib • Drug: Alectinib
6	Alectinib in Combination With Bevacizumab in ALK Positive NSCLC	• ALK gene rearrangement positive • Non-squamous non-small cell neoplasm of lung	• Drug: Alectinib • Drug: Bevacizumab
7	Crizotinib in Treating Patients With Stage IB-IIIA Non-small Cell Lung Cancer That Has Been Removed by Surgery and ALK Fusion Mutations (An ALCHEMIST Treatment Trial)	• ALK gene rearrangement • ALK gene translocation • ALK positive • Stage IB non-small cell lung carcinoma AJCC v7 • Stage II non-small cell lung cancer AJCC v7 • Stage IIA non-small cell lung carcinoma AJCC v7 • Stage IIB non-small cell lung carcinoma AJCC v7 • Stage IIIA non-small cell lung cancer AJCC v7	• Other: clinical observation • Drug: Crizotinib • Other: laboratory biomarker analysis

Table 3 (*continued*)

Table 3 (*continued*)

No.	Title	Conditions	Interventions
8	A Study of Usage of Brigatinib in the Treatment of Adult Participants for Approved Indications In South Korea	• Carcinoma, non-small cell lung • Anaplastic lymphoma kinase	• Other: no intervention
9	Basket Study of Entrectinib (RXDX-101) for the Treatment of Patients With Solid Tumors Harboring NTRK 1/2/3 (Trk A/B/C), ROS1, or ALK Gene Rearrangements (Fusions)	• Breast cancer • Cholangiocarcinoma • Colorectal cancer • Head and neck neoplasms • Lymphoma, large-cell, anaplastic • Melanoma • Neuroendocrine tumors • Non-small cell lung cancer • Ovarian cancer • Pancreatic cancer • and 6 more	• Drug: Entrectinib

ClinicalTrials.gov Search Results (search date: 04/30/22, total: 9 trials). ALK, anaplastic lymphoma kinase; NSCLC, non-small cell lung cancer; AJCC, American Joint Committee on Cancer.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-619/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-619/coif). CGL is employed by Bristol Myers Squibb. RADM serves as an unpaid editorial board member of *Translational Lung Cancer Research* from January 2020 to December 2023. RADM declares on the advisory board for Takeda; scientific sponsorship from Merck, Bayer and Pfizer; speaker fee from Novartis, Eurofarma, MSD, Astellas, and Astrazeneca; leadership for European School of Oncology. The other authors have no 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. The Global Cancer Observatory. Globocan2020 [Internet]. 2022 [cited 2022 Jan 29]. Available online: https://gco.iarc.fr/today/data/factsheets/cancers/15-Lung-fact-sheet.pdf
2. Iwama E, Okamoto I, Harada T, et al. Development of anaplastic lymphoma kinase (ALK) inhibitors and molecular diagnosis in ALK rearrangement-positive lung cancer. Onco Targets Ther 2014;7:375-85.
3. Toschi L, Rossi S, Finocchiaro G, et al. Non-small cell lung cancer treatment (r)evolution: ten years of advances and more to come. Ecancermedicalscience 2017;11:787.
4. Melosky B, Wheatley-Price P, Juergens RA, et al. The rapidly evolving landscape of novel targeted therapies in advanced non-small cell lung cancer. Lung Cancer 2021;160:136-51.
5. Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. N Engl J Med 2004;350:2129-39.
6. Gregg JP, Li T, Yoneda KY. Molecular testing strategies in non-small cell lung cancer: optimizing the diagnostic

journey. Transl Lung Cancer Res 2019;8:286-301.
7. Pikor LA, Ramnarine VR, Lam S, et al. Genetic alterations defining NSCLC subtypes and their therapeutic implications. Lung Cancer 2013;82:179-89.
8. Milne CP, Bryan C, Garafalo S, et al. Complementary versus companion diagnostics: apples and oranges? Biomark Med 2015;9:25-34.
9. FDA. List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools). Available online: https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools
10. Planchard D, Popat S, Kerr K, et al. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2018;29:iv192-237.
11. Kalemkerian GP, Narula N, Kennedy EB, et al. Association for Molecular Pathology Clinical Practice Guideline Update. 2018. Available online: https://doi.org/10.1200/JCO.2017
12. Mosele F, Remon J, Mateo J, et al. Recommendations for the use of next-generation sequencing (NGS) for patients with metastatic cancers: a report from the ESMO Precision Medicine Working Group. Ann Oncol 2020;31:1491-505.
13. Kim L, Tsao MS. Tumour tissue sampling for lung cancer management in the era of personalized therapy: What is good enough for molecular testing? European Respiratory Journal 2014;44:1011-22.
14. Canale M, Pasini L, Bronte G, et al. Role of liquid biopsy in oncogene-addicted non-small cell lung cancer. Transl Lung Cancer Res 2019;8:S265-79.
15. Leighl NB, Page RD, Raymond VM, et al. Clinical Utility of Comprehensive Cell-free DNA Analysis to Identify Genomic Biomarkers in Patients with Newly Diagnosed Metastatic Non-small Cell Lung Cancer. Clin Cancer Res 2019;25:4691-700.
16. Aggarwal C, Thompson JC, Black TA, et al. Clinical Implications of Plasma-Based Genotyping With the Delivery of Personalized Therapy in Metastatic Non-Small Cell Lung Cancer. JAMA Oncol 2019;5:173-80.
17. Mack PC, Banks KC, Espenschied CR, et al. Spectrum of driver mutations and clinical impact of circulating tumor DNA analysis in non-small cell lung cancer: Analysis of over 8000 cases. Cancer 2020;126:3219-28.
18. Zugazagoitia J, Ramos I, Trigo JM, et al. Clinical utility of plasma-based digital next-generation sequencing in patients with advance-stage lung adenocarcinomas with insufficient tumor samples for tissue genotyping. Ann Oncol 2019;30:290-6.
19. Remon J, Lacroix L, Jovelet C, et al. Real-World Utility of an Amplicon-Based Next-Generation Sequencing Liquid Biopsy for Broad Molecular Profiling in Patients With Advanced Non-Small-Cell Lung Cancer. JCO Precis Oncol 2019;3:PO.18.00211.
20. Hofman P. Detecting Resistance to Therapeutic ALK Inhibitors in Tumor Tissue and Liquid Biopsy Markers: An Update to a Clinical Routine Practice. Cells 2021;10:168.
21. Reclusa P, Laes JF, Malapelle U, et al. EML4-ALK translocation identification in RNA exosomal cargo (ExoALK) in NSCLC patients: a novel role for liquid biopsy. Transl Cancer Res 2019;8:S76-8.
22. Manicone M, Scaini MC, Rodriquenz MG, et al. Liquid biopsy for monitoring anaplastic lymphoma kinase inhibitors in non-small cell lung cancer: two cases compared. J Thorac Dis 2017;9:S1391-6.
23. Pisapia P, Malapelle U, Troncone G. Liquid Biopsy and Lung Cancer. Acta Cytol 2019;63:489-96.
24. Liam CK, Mallawathantri S, Fong KM. Is tissue still the issue in detecting molecular alterations in lung cancer? Respirology 2020;25:933-43.
25. Rolfo C, Mack PC, Scagliotti GV, et al. Liquid Biopsy for Advanced Non-Small Cell Lung Cancer (NSCLC): A Statement Paper from the IASLC. J Thorac Oncol 2018;13:1248-68.
26. Huang H. Anaplastic Lymphoma Kinase (ALK) Receptor Tyrosine Kinase: A Catalytic Receptor with Many Faces. Int J Mol Sci 2018;19:3448.
27. Soda M, Choi YL, Enomoto M, et al. Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. Nature 2007;448:561-6.
28. Rothenstein JM, Chooback N. ALK inhibitors, resistance development, clinical trials. Curr Oncol 2018;25:S59-67.
29. Christopoulos P, Kirchner M, Endris V, et al. EML4-ALK V3, treatment resistance, and survival: refining the diagnosis of ALK(+) NSCLC. J Thorac Dis 2018;10:S1989-91.
30. Iragavarapu C, Mustafa M, Akinleye A, et al. Novel ALK inhibitors in clinical use and development. J Hematol Oncol 2015;8:17.
31. Tsuyama N, Sakamoto K, Sakata S, et al. Anaplastic large cell lymphoma: pathology, genetics, and clinical aspects. J Clin Exp Hematop 2017;57:120-42.
32. Fujimoto J, Shiota M, Iwahara T, et al. Characterization of the transforming activity of p80, a hyperphosphorylated protein in a Ki-1 lymphoma cell line with chromosomal translocation t(2;5). Proc Natl Acad Sci U S A

1996;93:4181-6.
33. Bai RY, Dieter P, Peschel C, et al. Nucleophosmin-anaplastic lymphoma kinase of large-cell anaplastic lymphoma is a constitutively active tyrosine kinase that utilizes phospholipase C-gamma to mediate its mitogenicity. Mol Cell Biol 1998;18:6951-61.
34. Shaw AT, Kim DW, Nakagawa K, et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. N Engl J Med 2013;368:2385-94.
35. Gristina V, La Mantia M, Iacono F, et al. The Emerging Therapeutic Landscape of ALK Inhibitors in Non-Small Cell Lung Cancer. Pharmaceuticals (Basel) 2020;13:474.
36. Solomon BJ, Kim DW, Wu YL, et al. Final Overall Survival Analysis From a Study Comparing First-Line Crizotinib Versus Chemotherapy in ALK-Mutation-Positive Non-Small-Cell Lung Cancer. J Clin Oncol 2018;36:2251-8.
37. Solomon BJ, Mok T, Kim DW, et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. N Engl J Med 2014;371:2167-77.
38. Camidge DR, Kim HR, Ahn MJ, et al. Brigatinib Versus Crizotinib in ALK Inhibitor-Naive Advanced ALK-Positive NSCLC: Final Results of Phase 3 ALTA-1L Trial. J Thorac Oncol 2021;16:2091-108.
39. Hida T, Nokihara H, Kondo M, et al. Alectinib versus crizotinib in patients with ALK-positive non-small-cell lung cancer (J-ALEX): an open-label, randomised phase 3 trial. Lancet 2017;390:29-39.
40. Peters S, Camidge DR, Shaw AT, et al. Alectinib versus Crizotinib in Untreated ALK-Positive Non-Small-Cell Lung Cancer. N Engl J Med 2017;377:829-38.
41. Soria JC, Tan DSW, Chiari R, et al. First-line ceritinib versus platinum-based chemotherapy in advanced ALK-rearranged non-small-cell lung cancer (ASCEND-4): a randomised, open-label, phase 3 study. Lancet 2017;389:917-29.
42. Shaw AT, Bauer TM, de Marinis F, et al. First-Line Lorlatinib or Crizotinib in Advanced ALK-Positive Lung Cancer. N Engl J Med 2020;383:2018-29.
43. Solomon B, Bauer T, Mok T, et al. Abstract CT223: Updated efficacy and safety from the phase 3 CROWN study of first-line lorlatinib vs crizotinib in advanced anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC). Cancer Res 2022;82:CT223.
44. Horn L, Wang Z, Wu G, et al. Ensartinib vs Crizotinib for Patients With Anaplastic Lymphoma Kinase–Positive Non–Small Cell Lung Cancer. JAMA Oncol 2021;7:1617.
45. Patel MR, Bauer TM, Liu SV, et al. STARTRK-1: Phase 1/2a study of entrectinib, an oral Pan-Trk, ROS1, and ALK inhibitor, in patients with advanced solid tumors with relevant molecular alterations. J Clin Oncol 2015;33:2596.
46. Drilon A, Siena S, Ou SI, et al. Safety and Antitumor Activity of the Multitargeted Pan-TRK, ROS1, and ALK Inhibitor Entrectinib: Combined Results from Two Phase I Trials (ALKA-372-001 and STARTRK-1). Cancer Discov 2017;7:400-9.
47. Ceddia S, Codacci-Pisanelli G. Treatment of brain metastases in ALK-positive non-small cell lung cancer. Crit Rev Oncol Hematol 2021;165:103400.
48. Elsayed M, Christopoulos P. Therapeutic Sequencing in ALK(+) NSCLC. Pharmaceuticals (Basel) 2021;14:80.
49. Lin JJ, Jiang GY, Joshipura N, et al. Efficacy of Alectinib in Patients with ALK-Positive NSCLC and Symptomatic or Large CNS Metastases. J Thorac Oncol 2019;14:683-90.

Cite this article as: Zia V, Lengyel CG, Tajima CC, de Mello RA. Advancements of ALK inhibition of non-small cell lung cancer: a literature review. Transl Lung Cancer Res 2023;12(7):1563-1574. doi: 10.21037/tlcr-22-619