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REVIEW

Optimal Care for Patients with Anaplastic Lymphoma Kinase (ALK)–Positive Non–Small Cell Lung Cancer: A Review on the Role and Utility of ALK Inhibitors

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Abstract: The treatment of advanced non–small-cell lung cancer (NSCLC) has undergone a paradigm shift in the last decade. Molecular characterization of the disease has led to the rapid development of personalized medicine and swift delivery of targeted therapies to patients. The discovery of the anaplastic lymphoma kinase (*ALK)* gene in patients with NSCLC has resulted in rapid bench–bedside transition of several active drugs, with several others currently in clinical trials. After the first-generation ALK inhibitor crizotinib, next-generation ALK inhibitors have entered clinical applications for *ALK*-rearranged NSCLC. Ceritinib, alectinib, and brigatinib have all received approval for ALK-positive patients who have failed prior crizotinib, as well as first-line therapy in treatment-naïve patients based on favorable efficacy. Most recently, lorlatinib, a potent, newer-generation ALK inhibitor, has been approved as second- or third-line treatment. These advances have led to better patient outcomes, but concurrently have led to several crucial unanswered questions about optimal care for ALK-positive NSCLC patients. The ultimate acquisition of resistance to ALK-inhibitor therapy poses a challenge to ongoing research efforts, in addition to the routine management of these patients in the clinic. This review provides a summary of the clinical development of crizotinib, ceritinib, alectinib, brigatinib, and lorlatinib and highlights current management paradigms, current and evolving clinical information, emerging clinical decision-making and sequencing of therapy in advanced, metastatic, or recurrent ALK-positive NSCLC.

Keywords: non–small cell lung cancer, *ALK* rearrangement, crizotinib, ceritinib, alectinib, brigatinib, lorlatinib

Introduction

Lung cancer is the leading cause of cancer-related death in the US and worldwide, with <20% 5-year survival for newly diagnosed patients.[1] Lung cancers are classified into two main types: non–small cell lung cancer (NSCLC; 80%–85%) and small cell lung cancer (15%–20%).[2,3] NSCLCs are further subdivided into three main types: adenocarcinoma (50%), squamous-cell carcinomas (30%), and large-cell carcinomas.[4] Increased understanding of molecular and biological aspects of cancer growth has led to the discovery of several oncogenic driver mutations, thereby dramatically changing treatment paradigms for patients with NSCLC over the past decade. Genetic alterations, such as epidermal growth factor receptor

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(*EGFR)* mutations (10%–15% in NSCLC in Europe and North America) and anaplastic lymphoma kinase (*ALK)* rearrangement are two examples of the targets in NSCLC that have revolutionized the concept of precision oncology.[4–6] There can exist substantial variation in *EGFR*-mutation frequency when grouped by geographic region, and *EGFR*-mutation frequency has been reported to be 20%–76% in Asia–Pacific regions.[7] Rearrangement in ALK-receptor tyrosine kinase, a molecular subtype of NSCLC, occurs in 5%−7% of NSCLC patients.[8–11] While in unselected NSCLC patients, overall frequency of *ALK* rearrangement is low, selection of patients based on clinicopathological features, such as no or light smoking history and adenocarcinoma histology results in higher frequencies (about 13%) of *ALK*-rearranged NSCLC.[16] There are an estimated 40,000 incident cases of ALK-positive NSCLC worldwide each year, and patient characteristics are quite dissimilar from the overall patient population with NSCLC.[11] ALK-positive NSCLC patients are generally younger (median age 52 years old), are never- to only light smokers, and primarily have adenocarcinoma histology.[12–16] Clinicopathological findings of younger age, never- to light smoking history and adenocarcinoma-predominant histology in ALK-positive patients were confirmed in a large real-world retrospective analysis recently.[17]

ALK-gene alterations were first reported in the 1990s through the cloning of translocation involving the short arm of chromosome 2 and long arm of chromosome 5— t (2;5) — discovered in a small number of anaplastic large-cell lymphomas.[18,19] ALK translocation was next discovered in a subset of inflammatory myofibroblastic tumors,[20] and later in 2007 *ALK*-gene alternation/rearrangement was first described in patients with NSCLC.[20–22] In NSCLC, this gene alteration was reported as a small inversion within the short arm of chromosome 2 (2p) that juxtaposed the 5′ end of the echinoderm microtuble-associated protein-like 4 (*EML4)* gene with the 3′ end of the *ALK* gene, resulting in the fusion oncogene *EML4–ALK* in NSCLC cells. Formation of the EML4–ALK fusion leads to activation, thereby potentiating proliferation and survival of the cancer cells.[11,23] Diagnosis is most typically made using fluorescence in situ hybridization (FISH), immunohistochemistry (IHC), or next-generation sequencing (NGS) of the tumor tissue.[24,25] In the US, FISH, IHC, and NGS are approved companion diagnostic tests to identify ALK-positive NSCLC.[12]

ALK Inhibitors

Before the discovery of the EML4–ALK fusion protein, conventional chemotherapy was used as the first line of therapy for all advanced or metastatic NSCLC. After the EML4–ALK discovery, crizotinib (first generation of ALK-directed therapy), a tyrosine kinase inhibitor (TKI) targeting ALK, ROS1, and MET was tested in a phase I trial[26] and became the first US FDA-approved ALK inhibitor for NSCLC. Ceritinib was the first of the second-generation ALK inhibitors tested, and was later approved after confirmation of its efficacy in both crizotinib-resistant and crizotinib-naïve patients. Soon after, two other ALK inhibitors — alectinib and brigatinib — were approved for ALK-positive patients who had failed prior crizotinib. While both are now approved in treatment-naïve patients, alectinib has become the preferred agent. Most recently, we have started learning more about the indisputable role of lorlatinib, a highly potent, next-generation ALK/ROS1 TKI. However, the benefit of ALK TKIs is limited by the emergence of drug resistance. Several mechanisms of resistance to ALK TKIs have now been discovered. In this review, we discuss each of the ALK inhibitors, mechanisms of acquired resistance of cancer cells to each of these inhibitors, their effectiveness in cases with brain metastases, and their role in optimal care of patients with advanced or metastatic *ALK*-rearranged NSCLC.

Crizotinib

The promising results from the aforementioned phase I study[26] led to the phase III PROFILE 1007 trial, which compared crizotinib with either pemetrexed or docetaxel in the second-line setting in patients with locally advanced or metastatic *ALK*-rearranged NSCLC after progressing on one prior platinum-based regimen.[27] The primary end point of median progression-free survival (mPFS) was 7.7 months in the crizotinib group and 3.0 months in the pemetrexed or docetaxel group (for progression or death with crizotinib hazard ratio (HR) 0.49, 95% confidence interval (CI) 0.37–0.64; $p<0.001$). Prior to this, crizotinib had already received accelerated approval on August 26, 2011. Subsequently, the promising results from the PROFILE 1007 trial led to regular approval of crizotinib on November 20, 2013 in second line settings for *ALK*-rearranged lung cancer patients after progression on platinum doublet therapy.[28]

The key phase III PROFILE 1014 trial aimed to assess the efficacy of the ALK inhibitor crizotinib compared with standard chemotherapy (pemetrexed plus platinum) as first-line treatment for advanced *ALK*-rearranged NSCLC.[29] This trial established crizotinib's superiority over the standard first-line regimens. mPFS was significantly longer in the crizotinib arm (10.9 months) than the standard-chemotherapy arm (7 months; HR 0.45, 95% CI 0.35–0.60; $p<0.001$), and the overall response rate (ORR) was 74% in the crizotinib arm vs 45% in the standard-chemotherapy arm ($p<0.001$). Additionally, crizotinib was associated with greater reduction in lung cancer symptoms and improvement in quality of life. As a result of this study, crizotinib became the standard first-line agent in patients with ALK-positive NSCLC.[30] In 2014, the PARAMOUNT study demonstrated overall survival (OS) benefit with the use of maintenance pemetrexed in patients with advanced nonsquamous NSCLC.[31] These results were reported after the PROFILE 1014 trial had long been underway, but led to criticism of PROFILE 1014's study design, which lacked the use of maintenance pemetrexed in the standard-chemotherapy arm. Nonetheless, this trial highlighted OS benefit in crizotinib, with median OS not reached (NR) with crizotinib (95% CI 45.8 months to NR) and 47.5 months with chemotherapy (95% CI 32.2 months to NR, HR 0.76, 95% CI 0.548–1.053; $p=0.0978$), probably not reaching statistical significance due to crossover allowed as part of the study design.

Mechanisms of Acquired Resistance to Crizotinib

Patients on crizotinib can develop resistance and relapse, with isolated central nervous system (CNS) progression, extracranial oligoprogression, or systemic progression, usually after a year.[32] The mechanisms of relapse have been categorized as ALK-dependent and ALK-independent.[11] Generally, ALK-dependent resistance occurs as a result of secondary mutations within the target kinase that reinduce kinase activation, despite the presence of the TKI.[33] The emergence of secondary mutations hinder the binding of the TKI to the target kinase, and thus unchecked kinase activation ensues.

Around a third of secondary resistance mutations are located in the ALK tyrosine-kinase domain, with the commonest being L1196M.[34] L1196M-mutation resistance (observed in 7% of crizotinib-resistant cases) is followed closely by the G1269A mutation (4%). The G1202R mutation, observed in 2% of cases, confers high-level resistance to crizotinib, as well as to next-generation ALK inhibitors. A second ALK-dominant mechanism of crizotinib resistance is amplification of the *ALK*-fusion gene, which occurs less frequently than secondary mutation acquisition.[33,34] Non–ALK dominant mechanisms represent reactivation of bypass signaling pathways, such as EGFR, NRG1 overexpression, IGF-1R activation, or c-KIT, which prevent the tumor's dependence upon ALK activation for continued growth and survival.[35] These two main mechanisms of ALK-TKI resistance to crizotinib and other next-generation ALK TKIs are highlighted in Table 1.

The PROFILE trials demonstrated that crizotinib achieves higher responses in systemic lesions in *ALK*-rearranged NSCLC than chemotherapy. However, it was not clear if crizotinib was effective in CNS metastasis.[29,30,36] The brain is a common sanctuary site of metastatic disease progression for patients on crizotinib, with about 70% of patients

Table 1 Main Mechanisms of Resistance to First- and Next-Generation ALK TKIs

ALK TKIs[29,33,96,97]	ALK-Dependent Resistance Mechanism (Amplification/Mutation Acquisition)	ALK-Independent Resistance Mechanism (Bypass of Signaling Pathways)
Crizotinib	Amplification of the *ALK* fusion gene; L1196M, G1269A/S, I1151Tins, L1152P/R, C1156Y/T, I1171T/N/S, F1174C/L/V, V1180L, G1202R, S1206C/Y, E1210K mutation acquisition	EGFR, NRG1 overexpression,[101] IGF-1R activation[102]
Ceritinib	G1202R, F1174C/L/V, G1202del, I1151Tins, L1152P/R, C1156Y/T	*cMET*-gene amplification; activating mutation of *MEK* (*MAP2K1*^{K57N}), *PIK3CA* mutations
Alectinib	G1202R, I1171T/N/S, V1180L, L1196M	*cMET*-gene amplification, *PIK3CA mutations*
Brigatinib	E1210K + S1206C, E1210K + D1203N, G1202Ra	Not described
Lorlatinib[100]	L1198F + C1156Yc, L1196M/D1203N, F1174L/G1202R, C1156Y/G1269A	*NF2* loss-of-function mutations[100]

Abbreviation: TKI, tyrosine-kinase inhibitor.

experiencing CNS progression.[37,38] It is also known that crizotinib has a suboptimal effect on control of metastatic disease in the CNS.[39] Crizotinib is a known substrate of PgP, a key efflux pump in the blood–brain barrier (BBB), signifying that the BBB may preclude attainment of therapeutic levels in patients with CNS disease. Low concentrations of crizotinib in cerebrospinal fluid (CSF) compared with plasma-crizotinib concentrations have been demonstrated (lower CSF:plasma ratios, in the range of 0.06–0.26%). In animal models, the IC_{50} for crizotinib was determined to be 60–120 nM, which was well below the median steady-state plasma concentration of 570 nM/L achieved with the standard approved dose of 250 mg twice daily.[40,41] In addition, anecdotal reports have highlighted poor CSF concentration of a meager 1.4 nM/L, signifying inadequate levels of crizotinib in the CNS.[40,42] These findings explained the ineffectiveness of this drug in CNS metastatic disease.[42–44]

Ceritinib

In vitro enzymatic studies have demonstrated that ceritinib (a second-generation oral ALK inhibitor) is about 20 times as potent as crizotinib.[45,46] It does not inhibit activity of MET kinase; however, it has inhibitory properties against other kinases, such as ROS1 and IGF-1R.[47] It has demonstrated activity and efficacy against *ALK* mutations arising after crizotinib exposure, namely L1196M, G1269A, I1171T, and S1206Y,[48] but failed to overcome two crizotinib-resistant *ALK* mutations — G1202R and F1174C (as illustrated in Table 1).[46] In the phase I ASCEND-1 trial, 255 patients with locally advanced *ALK*-rearranged or metastatic NSCLC were enrolled. In the ALK-naïve patient population (n=83), ORR was noted to be 72% and median duration of response (DoR) 17 months. In the ALK inhibitor–pretreated patient cohort (n=163), ORR was noted to be 56% and median DoR 8.3 months. mPFS in ALK inhibitor-naïve patient population was 18.4 months and 6.9 months in patients with prior exposure to ALK inhibitors.[49] The phase II ASCEND-2 trial included 140 patients who had received two or more previous treatment regimens (with chemotherapy, one or more platinum doublets). The median DoR was 9.7 months and mPFS 5.7 months, similar to those reported in ASCEND-1.[50] The phase III ASCEND-5 trial evaluating ceritinib versus chemotherapy in patients with *ALK*-rearranged NSCLC (progressed on chemotherapy and crizotinib) met its primary end point of superior PFS in 231 patients with progressive disease (5.4 months for ceritinib vs 1.6 months for chemotherapy, HR 0.49,95% CI 0.36–0.67; $p<0.0001$).[51] In 2017, ASCEND-4, a global phase III trial, compared ceritinib with platinum–pemetrexed combination chemotherapy in newly diagnosed patients with metastatic *ALK*-rearranged NSCLC (n=376), demonstrating significant improvement in mPFS (16.6 months in the ceritinib arms vs 8.1 months in the chemotherapy arm, HR 0.55; $p<0.00001$).[52] The compelling results of ASCEND-4 led to US FDA approval of ceritinib 750 mg/day as a first-line agent in *ALK*-rearranged NSCLC on May 26, 2017. Later, in December 2017, the FDA-approved dose of ceritinib was changed from 750 mg/day under fasting conditions to 450 mg/day taken with food, based on the results of the ASCEND-8 study (a randomized phase I study of ceritinib 450 mg or 600 mg taken with a low-fat meal versus 750 mg in fasted state).[53] Ceritinib at 450 mg daily with food had similar plasma-drug concentrations and a more favorable gastrointestinal safety profile than ceritinib 750 mg daily in fasted patients, leading to the FDA decision to lower the ceritinib dose to 450 mg/day. In a recent safety and efficacy update on ASCEND-8, ceritinib at a dose of 450 mg with food showed consistent efficacy (shown in Table 2) and less gastrointestinal toxicity.[54]

In addition to being effective in the majority of patients who are resistant to crizotinib, ceritinib is also more efficacious than crizotinib in the treatment of brain metastasis. This was highlighted in the phase I and II trials ASCEND-1 and ASCEND-2, with ORR of 63% in patients who were ALK inhibitor–naïve (ASCEND-1)[49] and ORR of 45% in crizotinib-pretreated patients (ASCEND-2).[50] ASCEND-7 was designed specifically to study intracranial effects of ceritinib. This trial assigned patients based on prior treatment exposure. A total of 42 patients treated with an ALK inhibitor and brain radiotherapy were assigned to arm 1, 40 patients with prior ALK inhibitor only to arm 2, 12 patients with prior brain radiotherapy only to arm 3, and 44 patients not previously treated with brain radiotherapy or an ALK inhibitor to arm 4. In the recently reported results, intracranial ORRs of 39.3% (95% CI 21.5%–59.4%), 27.6% (95% CI 12.7%–47.2%), 28.6% (95% CI 3.7%–71.0%), and 51.5% (95% CI 33.5%–69.2%), respectively, for each of the four arms. This study confirmed the efficacy and safety of ceritinb in patients with active brain metastasis with or without a prior exposure to crizotinib.[55,56] Similar to crizotinib, the efficacy of ceritinib can also be hindered by emergence of secondary resistance mutations. G1202R (found in only 2% of post-crizotinib samples) is a predominant resistance mechanism post-ceritinib, -alectinib, and -brigatinib (frequency of 21%–43%).[34] Additionally, F1174 mutations also confer resistance to

Table 2 Major ALK-Inhibitor Clinical Trials for Second- and Next-Line Therapy in ALK-Rearranged Non–Small Cell Lung Cancer

Trial	PROFILE 1007[27]	ASCEND-5[51]	ASCEND-8[53,54]	NP28673[63]	ALTA[73]	Solomon et al[81]
ALK inhibitor	Crizotinib (n=173)	Ceritinib (n=115)	Ceritinib 450 mg with low-fat meal (n=108)	Alectinib (n=138)	Brigatinib 90 mg; arm A (n=112)	Lorlatinib 100 mg (n=276)[$]
Comparator	Chemotherapy–pemetrexed or docetaxel (n=174)	Chemotherapy–pemetrexed or docetaxel (n=116)	Ceritinib 750 mg, fasted (n=111)	None (single-arm study)	Brigatinib 180 mg; arm B (n=110)	None (single-arm study)
Primary end point	mPFS	mPFS	ORR	ORR	ORR	ORR
Response rate (%)	65 vs 20	39.1 vs 6.9	78.1% vs 75.7%	50	45 vs 54	EXP (2–3A) 69.5; EXP3B 32.1; EXP (4–5) 38.7
Median PFS (months)	7.7 vs 3 (HR 0.49, 95% CI 0.37–0.64; p<0.001)	5.4 vs 1.6 (HR 0.49, 95% CI 0.36–0.67; p<0.0001)	NE (95% CI 11.8–NE) vs 12.2 (8.2–NE); HR and p-value — NR	8.9 (95% CI 5.6–11.3)	9.2 vs 12.9 (HR 0.55, 95% CI 0.35–0.86, arm B vs A)	Pooled mPFS (EXP2–5): 7.3 (95% CI 5.6–11.0)
Median OS (months)	21.9 vs 21.7 (HR 0.85, 95% CI 0.66–1.10; p=0.11)	18.1 vs 20.1 (HR 1.00, 95% CI 0.67–1.49; p=0.50)	NR	Pooled analysis with another study (NP28761)[57], mOS 29.1 (95% CI 21.3–39.0)	27.6 vs NR (HR 0.67, 95% CI 0.42–1.06; p-value NR	NR

Notes: [$]ALK-positive and pretreated with crizotinib without chemotherapy (n=27; EXP2); ALK-positive and pretreated with crizotinib and chemotherapy (n=32; EXP3A); ALK-positive and one previous non–crizotinib ALK TKI with or without chemotherapy (n=28; EXP3B); ALK-positive and pretreated with two ALK TKIs with or without chemotherapy (n=66; EXP4); ALK-positive and pretreated with three ALK TKIs with or without chemotherapy (n=46; EXP5). Cohorts EXP1 (treatment-naïve ALK+) and EXP6 (ROS1$^+$) excluded in this table.

Abbreviations: mOS, median overall survival; mPFS, median progression-free survival; NR, not reported; NR, not reached; ORR, objective response rate.

ceritinib.[34] MEK reactivation is a key ALK-independent resistance mechanism post-ceritinib (Table 1).

Alectinib

Alectinib is a highly potent second-generation ALK-specific TKI and exhibits suppressive activity against RET kinase.[57,58] However, it lacks inhibitory properties against MET kinase and has little activity against ROS1 kinase.[59] In Japan, a phase I/II study of alectinib (AF-001JP) in ALK inhibitor–naïve *ALK*-rearranged NSCLC patients enrolled patients (n=24) in the phase I portion of the trial. A dose of 300 mg twice daily was identified as apt in the phase I portion (no dose-limiting toxicities or grade 4 adverse events with the maximal dose) and thus recommended for phase II.[60] An ORR of 93.5% (95% CI 82.1%–98.6%) was demonstrated in the 46 patients enrolled in the phase II portion. At the 3-year follow up of this study, reported in 2017, PFS was 62% (95% CI 45%–75%), OS rate 78%, and median PFS not reached.[61] In the studies that followed, 600 mg twice daily was recommended for phase II based on activity, tolerability, and pharmacokinetic data.[62] Efficacy of alectinib 600 mg twice daily was assessed in two phase II studies conducted in an *ALK*-rearranged, crizotinib-resistant patient population. The first of these two pilot phase II studies (NP28673) enrolled 138 patients, and showed an ORR of 50% (95% CI 41%–59%) with mPFS of 8.9 (95% CI 5.6–11.3) months.[63] The second trial (the North American NP28761) showed similar results, wherein 87 *ALK*-rearranged, crizotinib-resistant NSCLC patients were enrolled, demonstrating ORR of 48% (95% CI 36%–60%) and mPFS of 8.1 (95% CI 6.2–12.6) months.[64] The findings from these two pilot studies led to accelerated FDA approval of alectinib in the US in patients with *ALK*-rearranged, crizotinib-resistant NSCLC on December 11, 2015. After consistent benefit in phase II studies, more promising results for alectinib came to the forefront as a frontline therapy. The phase III J-ALEX trial included Japanese patients with ALK inhibitor–naïve *ALK* rearrangement–positive NSCLC who were randomized to either alectinib at 300 mg twice daily or crizotinib 250 mg twice daily as first-line therapy.[65] This trial enrolled 207 patients, and mPFS was 34.1 months for alectinib (recent update,[66] 95% CI 22.1–NE) and 10.2 months for crizotinib (95% CI 8.2–12; HR0.37, 95% CI 0.26–0.52; p<0.0001). The similar global phase III ALEX trial compared

alectinib with crizotinib in treatment-naïve, advanced *ALK*-rearranged NSCLC patients.[67] This trial enrolled a total of 303 patients (including those with asymptomatic CNS disease) randomized to receive either alectinib 600 mg twice daily or crizotinib 250 mg twice daily. mPFS in the alectinib arm was superior to crizotinib arm (34.8 months vs 10.9 months, HR 0.50, 95% CI 0.36–0.70; $p<0.001$) in a recent update.[68] Despite alectinib dose disparity in both ALEX trials, the superiority of alectinib over crizotinib was evident. Following this, alectinib was FDA-approved for first-line treatment of *ALK*-rearranged NSCLC on November 6, 2017 at a recommended dose of 600 mg orally twice daily with food.

In terms of activity against brain metastases, alectinib has proven superior to both crizotinib and ceritinib. Alectinib is not a substrate of PgP (unlike crizotinib and ceritinib), an essential efflux transporter located at the BBB. Alectinib was thus mechanistically thought to be a better penetrant of the BBB. A pooled analysis of two phase II studies showed an intracranial ORR of 64% (22% complete response) observed in 50 patients with measurable CNS disease.[69] In the ALEX trial, CNS-disease progression was more common in the crizotinib group as compared with the patient before enrollment, thereby making it possible to measure response to treatment in patients with baseline CNS disease: 59% of patients in the alectinib arm had a CNS response duration of >12 months compared with only 36% in the crizotinib arm.[67] In a recent update, for those with CNS metastases, mPFS was 25.4 months for alectinib versus 7.4 months for crizotinib (HR 0.37, 95% CI 0.23–0.58).[70]

In addition to activity against L1196M-gatekeeper mutation, alectinib is also active against other secondary mutations, such as G1269A.[34,57] Unfortunately, similarly to crizotinib and ceritinib, eventual resistance to alectinib is unavoidable. Common mutations seen after alectinib treatment are G1202R (as seen in ceritinib), I1171T/N/S (also seen post-crizotinib in 2% and ceritinib in 4% of cases), in addition to smaller percentages of a few others such as V1180L and L1196M (Table 1).[34] Genotyping results of paired tissue and plasma samples has demonstrated that G1202R, I1171T/N/S, and V1180L were prevalent at comparable percentages in both plasma and tissue samples; however, L1196M prevalence was much lower in tissue (2%) samples than in plasma (22%) genotyped samples.[71] L1196M-mutation paucity in tissue samples was believed to be residual from prior crizotinib exposure (as L1196M is the gatekeeper mutation that confers resistance to crizotinib), which likely was overcome by subsequent alectinib use. Overall, this suggests that the proportion of patients relapsing on alectinib due to secondary resistance mutations was similar between tissue and plasma samples. Therefore, it may be reasonable to detect putative resistance mutations in plasma upon progression on alectinib.

Brigatinib

Brigatinib, another second-generation ALK inhibitor, differs from others in its wide range of inhibitory properties against tumors with resistance-associated mutations.[43,72,73] Brigatinib effectively inhibits ALK and ROS1, with higher selectivity over more than 250 kinases and also may have a role in treating osimertinib-refractory *EGFR*-mutant NSCLC as it inhibits C797S–T790M–activating-mutation (triple mutation)–mediated EGFR-TKI resistance in vitro and in vivo.[74] In a study by Zhang et al, cellular and in vivo activities of ALK TKIs were compared using engineered and cancer-derived cell lines.[75] This study demonstrated superior in vitro and in vivo potency of brigatinib compared with crizotinib (12-fold greater potency than crizotinib). The study also demonstrated a superior inhibitory profile against all known 17 secondary *ALK* mutations (including G1202R) tested in cellular assays and higher inhibitory properties compared with crizotinib, ceritinib, and alectinib. The role of this is yet to be determined in daily practice; however, there appears to be a signal in initial trials indicating favorable results.

After an earlier phase I/II trial,[76] the randomized phase II ALTA trial enrolled crizotinib-resistant patients (n=222, 74% were recipients of prior chemotherapy) with advanced *ALK*-rearranged NSCLC.[73] The primary end point ORR was 54% (similar to ceritinib and alectinib), but mPFS was 12.9 months (better than ceritinib and alectinib). Of note, mPFS with brigatinib when assessed by an independent review board was 15.6 months. Although cross-trial comparisons can be deceptive, brigatinib seems to have a PFS advantage over ceritinib and alectinib. This superior PFS may correspond to expanded inhibition of developed ALK resistance, but brigatinib's efficacy after progression on alectinib and ceritinib remains to be determined. In a multicenter retrospective analysis, brigatinib demonstrated limited clinical activity in alectinib-refractory ALK-positive NSCLC.[77] Nonetheless, a phase II, open-label, single-arm, multicenter, international trial (NCT03535740) designed to assess the efficacy and safety of brigatinib in patients with ALK-positive NSCLC that have progressed on alectinib or ceritinib is under way.[78]

In addition, brigatinib has notable CNS activity in spite of being a substrate for PgP. In the aforementioned phase II ALTA trial, in patients with prior exposure to crizotinib, 69%

had CNS disease at baseline. The trial demonstrated ORR of 67% and median duration of CNS response of 16.6 months. In patients with any CNS disease at baseline, independent review board–assessed intracranial mPFS was 18.4 months. It received accelerated FDA approval on April 28, 2017 for *ALK*-rearranged NSCLC in patients who have progressed or are intolerant to crizotinib. ALTA-1L, the phase III trial, compared brigatinib with crizotinib in ALK inhibitor-–naïve *ALK* rearrangement–positive NSCLC to assess brigatinib's role in the first-line setting. mPFS was not reached in the brigatinib arm at the time of data analysis or 9.8 months (9.0–12.9) in the crizotinib arm (HR for disease progression or death 0.49 [95% CI 0.33−0.74]; 12-month PFS 67% [95% CI 56%–75%] for brigatinib versus 43% [95% CI 32%–53%] for crizotinib).[79] Based on these results, the FDA recently approved brigatinib for the first-line treatment of patients with ALK-positive metastatic NSCLC on May 22, 2020.

Lorlatinib

Lorlatinib, a third-generation ALK inhibitor, was designed specifically to target mutations that drive resistance to other ALK inhibitors and to penetrate the BBB. This macrocyclic TKI of ALK and ROS1 effectively penetrates the BBB and retains potency against most ALK-resistance mutations known to develop during treatment with crizotinib and next-generation TKIs, including the G1202R solvent-front mutation.[34,80,81] In the phase I portion of a phase I/II study,[81,82] lorlatinib demonstrated high efficacy, with 46% of patients with ALK-positive NSCLC achieving objective and durable responses (median DoR 12.4 months), many of whom had been recipients of several prior lines of therapy and had CNS involvement. Responses were evaluated for those patients who had received a second-generation TKI previously, as well as those who had prior exposure to crizotinib only. In addition, analysis of paired CSF and plasma samples showed high drug penetration into the CSF. This was demonstrated by pharmacokinetic analyses of paired blood and CSF, which demonstrated that the average ratio of CSF:plasma concentration of lorlatinib was 0.75 (75%), higher than the 0.03 ratio reported with crizotinib.[82] On the basis of phase I and preliminary phase II data, accelerated approval from the FDA was granted to lorlatinib on November 2, 2018 for the treatment of patients with *ALK*-rearranged advanced NSCLC after progression on crizotinib and at least one other ALK inhibitor. In a recent global phase II trial, lorlatinib demonstrated high intracranial activity in patients with advanced *ALK*-rearranged NSCLC who had been recipients of either crizotinib or other ALK inhibitors or were treatment-naïve.[81] The study enrolled 276 patients with histologically or cytologically *ALK*-rearranged or ROS1-positive advanced NSCLC with or without CNS disease, and assigned them to six experimental cohorts (EXP1–6) on the basis of prior therapy and ALK/ROS1 positivity.

The primary end point was response — overall and intracranial. In treatment-naïve patients (EXP1), objective response was achieved in 27 of 30. Three patients in this cohort had measurable baseline CNS lesions per independent centralized review, and intracranial tumor responses were observed in two (66.7%, 95% CI 9.4%–99.2%). ORR was 69% in crizotinib-treated patients, 33% in those treated with a non-crizotinib ALK inhibitor, and 39% in those treated with two or three previous ALK inhibitors. Lorlatinib thus represents an effective treatment strategy in heavily pretreated *ALK*-rearranged NSCLC patients and holds promise in the frontline setting. The future role of lorlatinib as a potent ALK inhibitor is promising. There exists a clear place for lorlatinib in the treatment of previously treated or refractory ALK-positive disease. The role of lorlatinib as first-line therapy was not answered in the first presented studies. The phase III CROWN trial comparing lorlatinib with crizotinib as first-line therapy is ongoing (NCT03052608), and results are eagerly awaited.

Sequence of Therapy

After progression on crizotinib, second-generation TKIs (ceritinib, alectinib, and brigatinib) were being used as second-line therapy. However, more recently the treatment paradigms have shifted, raising questions about the most optimal first-line therapy and selection of next-line therapies. Table 3 summarizes the results from ALK inhibitors as first-line therapy in trials of crizotinib (PROFILE 1014),[29] ceritinib (ASCEND-4),[52] alectinib (J-ALEX and ALEX),[65,67] and brigatinib (ALTA-1L).[79] Based on these results, alectinib has been widely adopted so far as a preferred first-line therapy for newly diagnosed *ALK*-rearranged NSCLC patients, due to its efficacy (including CNS activity) and safety profile. The National Comprehensive Cancer Network recommends use of any first- (crizotinib) or second-generation TKI (alectinib, ceritinib, or brigatinib) as first-line therapy for newly diagnosed *ALK*-rearranged NSCLC patients.[83] Treatment selection is also likely based on the experience and preference of the prescribing oncologist, as well as concerns for toxicity and tolerability. Table 2 lists the pivotal trials that led to the (mostly initial) approval of the five ALK inhibitors discussed herein in second-line or above settings. Table 4 highlights the efficacy of these ALK inhibitors for brain metastases in patients with *ALK*-rearranged NSCLC.

Table 3 Major ALK Inhibitor Clinical Trials for First-Line Therapy in ALK-Rearranged Non–Small Cell Lung Cancer

Trial	PROFILE 1014[29]	ASCEND-4[52]	J-ALEX[65]	ALEX[67]	ALTA 1L[79]
ALK inhibitor	Crizotinib (n=172)	Ceritinib (n=189)	Alectinib (n=103)	Alectinib (n=152)	Brigatinib (n=137)
Comparator	Platinum-based chemotherapy (n=171)	Platinum-based chemotherapy (n=187)	Crizotinib (n=104)	Crizotinib (n=151)	Crizotinb (n=138)
Primary end point	Median PFS (months)	Median PFS (months)	Median PFS (months)	Median PFS (months)	Median PFS (months)
Response rate (%)	74 vs 45	72.5 vs 26.7	Not reported	82.9 vs 75.5	71 vs 60
Median PFS (months)	10.9 vs 7 (HR 0.45, 95% CI 0.35–0.60; $p<0.001$)	16.6 vs 8.1 (HR 0.55, 95% CI 0.42–0.73; $p<0.00001$)	34.1 vs 10.2 (HR 0.37, 95% CI 0.26–0.52; $p<0.0001$)	34.8 vs 10.9 (HR 0.43, 95% CI 0.32–0.58; $p<0.01$)	Not reached vs 9.8 (HR 0.49, 95% CI 0.33–0.74; $p=0.0007$)
Median OS (months)	Not reached vs 47.5 (HR 0.76, 95% CI 0.548–1.05; $p=0.0978$	Not reached vs 26.2 (HR 0.73, 95% CI 0.5–1.08; $p=0.056$	—	Not reached vs not reached (HR 0.76, 95% CI 0.50–1.15)	—

Abbreviations: OS, overall survival; PFS, progression-free survival.

Table 4 Efficacy of Various ALK Inhibitors for Brain Metastases in Patients with *ALK*-Rearranged NSCLC

Trial	PROFILE 1007[27]	ASCEND-4[52]	ALEX[67]	ALTA[73]	Solomon et al[81]
ALK inhibitor (ALKi)	Crizotinib	Ceritinib	Alectinib	Brigatinib 90 mg; arm A	Lorlatinib 100 mg
Comparator	Chemotherapy–Pemetrexed or Docetaxel	Chemotherapy-Platinum based plus pemetrexed	Crizotinib	Brigatinib 180 mg; arm B	None (single-arm study)
Prior ALKi	ALKi-naïve	ALKi-naïve	ALKi-naïve	ALKi-pretreated	ALKi-pretreated
ICC-ORR	18%	73%	81%	42% in arm A; 67% in arm B	39%
IC-DoR	26.4 weeks	Not reported	17.3 months for patients with measurable target BM and NR for all patients with BM at baseline	NR (3.7 months–NR) for arm A; 16.6 (5.6 months–NR for arm B)	Not reported
Attainable CSF concentration and CSF to plasma ratio					
	Crizotinib	**Ceritinib**	**Alectinib**	**Brigatinib**	**Lorlatinib**
Attainable CSF concentration (nM/L)	1.4[35,37]	NA	2.7	NA	NA
CSF:plasma ratio	~0.003	NA	~0.75[40,98]	0.31[40]	0.75[99]

Abbreviations: BM, brain metastasis; NA, not available; NR, not reached; IC-DoR, intracranial duration of response; IC-ORR, intracranial objective response rate.

However, as discussed, numerous ALK-resistant mutations arise after treatment with these TKIs,[34] raising concerns for optimal sequencing of therapy. Tumor progression on crizotinib is inevitable and common with other ALK inhibitors as well. It has also been reported that patients who have progressive disease on second-generation ALK inhibitors have a higher likelihood of

harboring ALK-resistance mutations in their tumors than patients who have disease progression on crizotinib.[34,84] The most commonly reported *ALK* mutation is the solvent-front mutation G1202R, found in 56% of patients who progress on second-generation ALK inhibitors.[34] Insight into acquired mutation patterns upon progression can help with sequencing of therapy. As an example, patients that progress on ceritinib acquiring the F1174C mutation may benefit from alectinib, and those with acquired V1180L mutation on alectinib may benefit from brigatinib (Table 1 illustrates putative resistance-mutation patterns for different TKIs). Until recently, limited data regarding treatment of patients previously treated with different ALK inhibitors existed, but recent results from a global phase II study of the third-generation ALK inhibitor lorlatinib showed a high ORR and high intracranial response rate for patients with advanced ALK-positive NSCLC.[81] Lorlatinib was developed to better penetrate the BBB and remain potent to acquired resistant mutations that developed during therapy with first- and second-generation agents (particularly ALK^{G1202R} mutations). The fact that the solvent-front mutation G1202R is a resistant mutation acquired in most second-generation TKIs offers lorlatinib an indisputable role in patients progressed on several lines of TKI. In addition to targeting resistance mutations via use of new-generation TKIs for ALK-dependent tumors, improved understanding of basic mechanisms of ALK-independent resistance pathways are now informing the development of therapeutic strategies to counter resistance in the clinic. For instance, NRG1 (the ligand for HER3 and HER4 tyrosine kinases) overexpression can be abrogated by combined inhibition of ALK and HER2.[33] Similarly, MEK reactivation is an essential ALK-independent resistance mechanism post-ceritinib.[85] Combination with ALK and MEK inhibitors have reportedly resulted in improved responses, durability of response, and importantly suppression of TKI resistance.[33]

It should be pointed out that the identification of ALK-resistance mutations underlies the importance of obtaining rebiopsy upon disease progression, either by tissue or liquid form, to guide further appropriate TKI treatment while gaining better understanding of resistance mechanisms. Validation studies testing for *ALK* mutations in liquid form have been conducted and are being utilized at some centers. Recently, a multicenter collaborative study utilized liquid-biopsy technology and found molecular aberrations at a rate at least as high as standard-of-care tissue genotyping, with high tissue concordance.[86] The overall concordance rate for ALK fusion was reported at 99%, with a positive predictive value of 100%. The sensitivity of liquid biopsy for detection of ALK fusion was 75%, with a false-negative rate (1 – sensitivity) of 25%. These findings, though not perfect, are definitely encouraging. Few shortcomings need to be improved upon before liquid testing for detection of molecular aberrations becomes a standard tool for monitoring patients on treatment and selecting the next therapeutic options. Until then, tissue genotyping remains the standard of care. Liquid biopsy can be particularly valuable when tissue for genotyping is insufficient, significant delays in diagnosis are expected, or contraindications to the tissue biopsy exist.

Figure 1 illustrates a current proposed treatment algorithm for *ALK*-rearranged NSCLC. The proposed algorithm is based on the recent data reviewed so far in this paper within the framework in accordance with National Comprehensive Cancer Network[83] and European Society for Medical Oncology guidelines[87] and provides a useful treatment strategy in real-world practice. Our preference is to utilize rebiopsy-directed mutation-specific ALK inhibitors upon progression on first-line therapy, followed by lorlatinib (if not used previously) upon progression on mutation-specific TKIs. After progression on one or more second-generation TKIs, greater efficacy (ORR 62% and mPFS 7.3 months) of lorlatinib in patients with *ALK* mutations has been reported when compared with patients without *ALK* mutations.[88] This is likely due to less ALK dependence in the absence of putative mutations. In the absence of resistance mutation (and in the absence of alternate ALK-independent resistance pathways), upon progression on first-line TKIs, our preferred drug is lorlatinib as next-line therapy, due to evidence that suggests that even in mutation-negative patients, reasonable response rates (ORR 32%) and mPFS of 5.5 months can be attained.[88] Additionally, in patients with crizotinib-resistant disease, the efficacy of lorlatinib is comparable among patients with and without *ALK* mutations.[88] Nonetheless, further research is warranted to guide better treatment decision-making in patients with and without ALK-resistance mutations. Here again, the importance of rebiopsy, whether tissue- or liquid-based, upon each episode of progression cannot be emphasized more, so long as it is feasible in practice. The National Cancer Institute's ALK Master Protocol (NCT03737994) will prospectively match patients to appropriate ALK TKIs on the basis of the underlying ALK-resistance mutation.[89] Once patients have progressed on lorlaitnib, the next line of therapy is chemotherapy with or without immunotherapy or consideration of participation in available clinical trials.

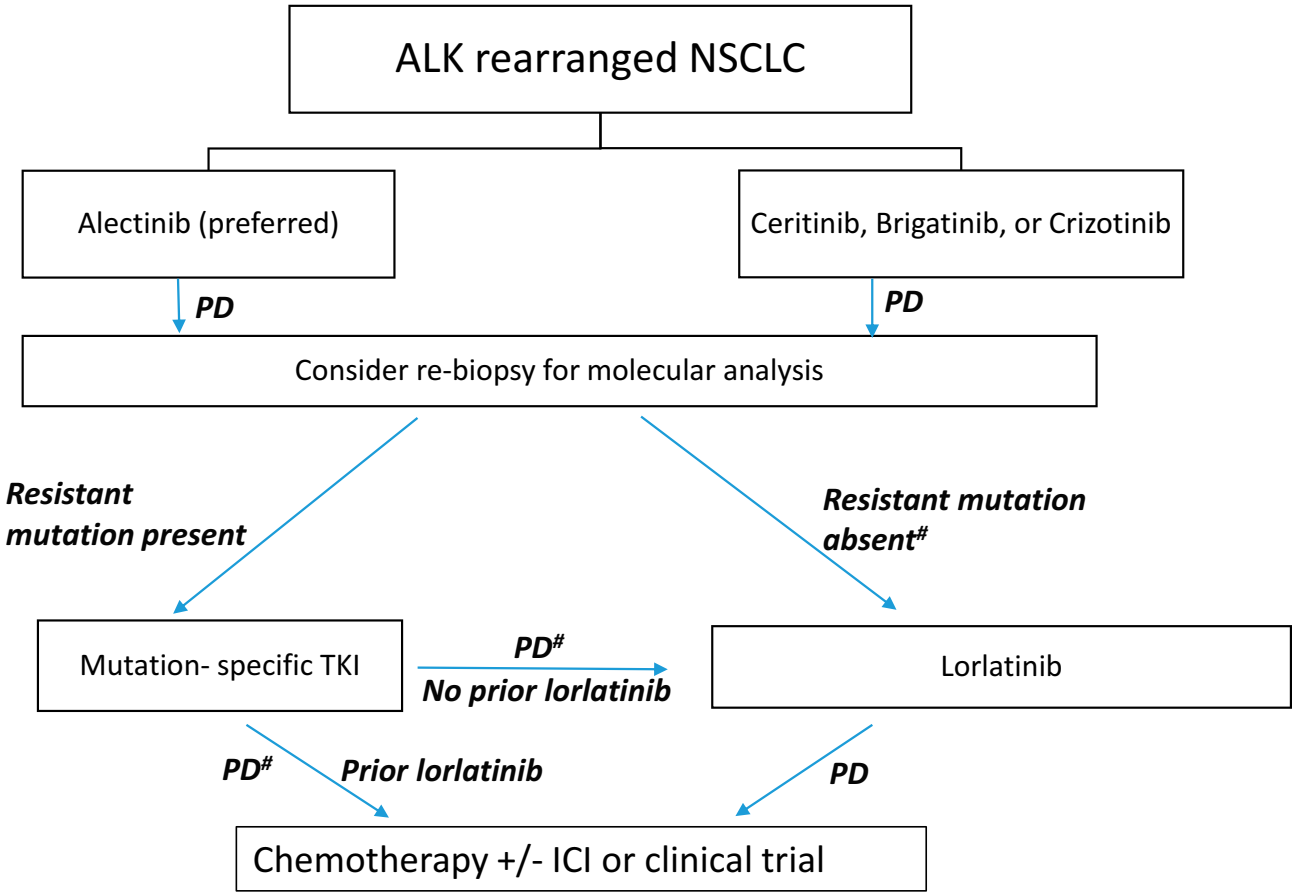

Figure 1 Treatment algorithm for *ALK*-rearranged non–small cell lung cancer.
Note: #Absence of ALK-dependent secondary mutations as well as ALK-independent alternate resistance pathways on rebiopsy.
Abbreviations: ICI, immunocheckpoint inhibitor; PD, progressive disease; TKI, tyrosine-kinase inhibitor.

Prospective Inhibitors and Trials in Progress

Enthusiasm for the new ALK inhibitors is high, and several new ALK inhibitors are in the pipeline. The ALK inhibitor ensartinib (X396) has shown activity and is well tolerated in *ALK*-rearranged NSCLC.[90] Additionally, phase III frontline studies, eg, comparing lorlatinib with crizotinib in the CROWN trial, are ongoing. However, there remains an unmet need to know more about on-target resistance mechanisms to the different ALK inhibitors. There also exists a need to understand off-target mechanisms underlying activation of alternate targetable molecular pathways during therapy with different ALK inhibitors. As such, the potential of eventually combining an ALK inhibitor with another targeted agent(s) might also be relevant in future to prevent or delay the development of resistance. Currently, the role of immunotherapy in combination with ALK inhibition is uncertain and not being studied actively. For example, a phase I/II trial in *ALK*-rearranged NSCLC patients evaluating a combination of ensartinib and durvalumab (NCT02898116) was terminated after enrolling just two patients, due to poor accrual. Another phase I/II study of nivolumab plus crizotinib for first-line treatment of ALK translocation–positive advanced NSCLC (CheckMate 370) was also closed prematurely, due to severe hepatotoxicity.[91] In the adjuvant setting, crizotinib is being studied after surgery for patients with stage IB–IIIA NSCLC in the ALCHEMIST trial (NCT02201992).[92] Another study in the adjuvant setting is evaluating the efficacy of alectinib versus standard adjuvant platinum-based chemotherapy (NCT03456076).[93] Other studies (NCT03088930, NCT04197076) evaluating ALK inihibitors in the neoadjuvant setting are also under way.[94,95]

Conclusion

Treatment options for *ALK*-rearranged NSCLC patients have advanced considerably in the past decade. Since the approval of the first ALK inhibitor, crizotinib, several newer generations

of ALK inhibitors have proven their supremacy as first-line therapies and have efficacy against crizotinib resistance. Such factors as ability to overcome resistance-associated mutations and enhanced CNS penetration have played a crucial role in improving efficacy. Many of the agents have received accelerated FDA approval in recent years, and it will be prudent to study postmarketing survival trends of these drugs in the real world, as well as compare approved inhibitors head to head to better select front-line therapies for patients. Many such initiatives are under way, as discussed. However, while we are awaiting the results of future studies, it is reasonable to conclude that the recent rapid progress in *ALK*-rearranged NSCLC treatment has clearly shown incremental benefits to patients with ALK-positive NSCLC by providing more effective and less toxic therapy.

Disclosure

The authors report no conflicts of interest in this work.

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