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The Current Landscape of Anaplastic Lymphoma Kinase (*ALK*) in Non-Small Cell Lung Cancer: Emerging Treatment Paradigms and Future Directions

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Abstract

Tumorigenic rearrangements in anaplastic lymphoma kinase (*ALK*) account for 3–7% of all non-small cell lung cancers (NSCLC). Treatment with targeted tyrosine kinase inhibitors (TKIs) has shown impressive clinical responses. Crizotinib was the first agent approved for front-line therapy of *ALK*-rearranged NSCLC after it demonstrated superiority to chemotherapy in response rate, duration of response, and progression-free survival. However, eventually all patients progress on crizotinib therapy, with the central nervous system (CNS) being the most common site, which served as the impetus for the development of more potent next-generation *ALK* inhibitors. Currently, ceritinib, alectinib, and brigatinib are all approved for second-line therapy after progression on or intolerance to crizotinib. Investigations into whether the initiation of a second-generation *ALK* inhibitor as first-line therapy is the superior treatment paradigm has resulted in the approval of ceritinib as initial therapy. Alectinib has also shown impressive results as front-line therapy, as recently reported in two large randomized studies that compared it to crizotinib. There is a significant need to better understand the drivers of and mechanisms underlying resistance to *ALK* inhibitors. While specific mutations have been identified, there is currently only limited evidence that the identification of specific mutations should impact selection of the next *ALK* inhibitor. The best treatment option for patients who become TKI refractory is also unclear, though there is some evidence to suggest that these patients are not responsive to checkpoint inhibitors and may respond better to chemotherapy. Combination therapy with other classes of agents may help to overcome resistance mechanisms and should be investigated further.

1 Introduction

Advances in genetic sequencing have revealed that non-small cell lung cancer (NSCLC), previously thought of as a homogenous disease, is actually comprised of multiple genetically distinct entities. This is especially true in adenocarcinoma, where multiple oncogenic ‘driver’ mutations have been identified. These mutations lead to downstream activation of

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canonical growth pathways, ultimately resulting in tumorigenesis. The use of targeted inhibitors has revolutionized the therapy for advanced NSCLC that harbor these mutations.

ALK (anaplastic lymphoma kinase) rearrangements are the driver mutation in 3–7% of NSCLC [1] with *EML4* (echinoderm microtubule-associated protein-like 4) as the most common fusion partner. Soda et al. were the first to demonstrate that *EML4-ALK* fusion was a distinct oncogenic event in a subset of NSCLC [2]. The fusion proteins lead to constitutive activity of the *ALK* tyrosine kinase. Several variants of *EML4-ALK* gene rearrangement based on the location in the *EML4* gene involved in the rearrangement have been described, including variant 1 in which the rearrangement occurs with exon 13 of the *EML4* gene fused to exon 20 of the *ALK* gene (E13:A20), variant 2 (E20:A20) and variant 3a/b (E6a/b:A20). In a retrospective analysis of 35 patients, Yoshida et al. showed that efficacy with crizotinib may vary based on the variant in a patient's tumor, with longer progression-free survival (PFS) observed in patients with variant 1 *EML4-ALK* gene rearrangement [3]. Whether these variants influence the activity of the next generation of *ALK* inhibitors is unknown. Also Ou et al. recently reported that the emergence of *ALK*-resistant mutations occurred more commonly in patients with variant 3 *EML4-ALK* rearrangement than in patients with variant 1 tumors [4]. Other rarer *ALK* fusions occur such as *KIF5B-ALK* [5], *KLC1-ALK* [6], and *ALK-PTPN3* [7], but they collectively are less frequent than the *ALK-EML4* rearrangement [8], and therefore little is known about their clinical significance with respects to different response to *ALK* TKIs. In general, patients with *ALK*-rearranged NSCLC tend to be younger, never smokers, and have lung adenocarcinoma, though rarely patients with other lung cancer histologies have also been found to harbor this mutation [9]. Unlike mutations in *EGFR* (epidermal growth factor receptor), where the incidence is higher in patients of Asian descent, the incidence of *ALK* rearrangements appears to be similar between Western and Asian patients [10]. Other driver mutations rarely co-exist with *ALK* rearrangements in NSCLC.

2 Testing for Anaplastic Lymphoma Kinase (*ALK*)

Fluorescence in situ hybridization (FISH) is the current gold standard to detect *ALK* gene rearrangements [11]. It utilizes complementary DNA probes to the 3' and 5' ends that are then visualized with fluorescent microscopy, with a focus on chromosome 2p23, which is the location of the *ALK* gene. In the native state, the 2p23 region will be seen as either a fusion of two signals or two immediately adjacent signals. Due to its inversion nature, an *ALK* rearrangement is detected if the two signals are split and are less than two signal distances apart [12]. A joint guideline from the College of American Pathologists, International Association for the Study of Lung Cancer (IASLC), and Association for Molecular Pathology defines a positive *ALK* FISH as 15% of 50 nuclei assessed demonstrating the classic splitsignal pattern. Interpretation should occur in areas with good signal, defined as where at least 50% of nuclei are easily analyzable [13]. The Vysis *ALK* FISH probe kit is US Food and Drug Administration (FDA) approved for the detection of *ALK* rearrangement. In this assay, a sample is considered to be positive for *ALK* if >25/50 cells demonstrate the classic signal and negative if <5/50 cells show the signal. In cases where 5–25 cells are positive, it is recommended to add both count readings and calculate an average percentage. If the average percentage is 15%, then the sample is considered

positive. Immunohistochemistry (IHC) is a more readily available test and can be used to screen for *ALK* rearrangements, especially as novel antibodies have been developed against chimeric *ALK* proteins. However, some have raised concerns about the IHC test. Cabillic et al. showed that there was significant discordance between FISH and IHC when they conducted parallel testing on the same samples. Of 3244 cases, 150 were found to be *ALK* positive by FISH and/or positive by IHC, but only 80 of those samples were found to be positive by both FISH and IHC. They concluded that one-quarter of *ALK*-positive samples would have been missed had only single FISH or IHC testing been employed [14]. Both these tests are approved for the diagnosis of *ALK*-positive patients and most institutions use one of the two tests. Some institutions will confirm the IHC positive result with a FISH test. Reverse transcription–polymerase chain reactions (RT-PCR) and next-generation sequencing (NGS) panels are also being used to detect the presence of a variety of potentially targetable mutations. The National Comprehensive Cancer Network (NCCN) guidelines currently recommend confirming the presence of *ALK* rearrangements using FISH if the initial screen with IHC returned positive. While there are no specific guidelines regarding the use of NGS, it appears to be as sensitive a method as FISH for detecting the presence of *ALK* rearrangements [15].

3 Therapeutic Options

3.1 Crizotinib

Crizotinib is a small-molecule tyrosine kinase inhibitor (TKI) of *ALK*, *c-MET*, and *ROS-1*. Camidge et al. were the first to report from an expansion phase I trial (PROFILE 1001) that it was a tolerable and safe drug that resulted in durable responses in patients with *ALK*-rearranged NSCLC [16]. Shaw et al. showed in a randomized phase III trial (PROFILE 1007) that in patients with advanced *ALK*-rearranged NSCLC that had progression after platinum-based chemotherapy, treatment with crizotinib led to improved PFS compared to chemotherapy [17]. There was a significantly higher response rate to crizotinib (65%) versus chemotherapy (20%). In another randomized phase III trial, Solomon et al. demonstrated the superiority of crizotinib over standard platinum doublet chemotherapy as first-line therapy for *ALK*-rearranged NSCLC in PROFILE 1014 [18]. In this study, the median PFS (mPFS) for crizotinib was 10.9 months compared with 7.0 months for chemotherapy (hazard ratio [HR] 0.45, $p < 0.001$). There was a higher response rate with crizotinib (74%) than with chemotherapy (45%, $p < 0.001$). Response was also more durable on crizotinib (11.3 vs. 5.3 months). There was no difference in overall survival (OS) between the two groups, which is likely due to 70% of patients in the chemotherapy group crossing over to the crizotinib group. As a result of these studies, crizotinib is approved in the USA, European Union (EU), and Japan as front-line therapy for patients with advanced *ALK*-rearranged NSCLC at a dose of 250 mg orally twice daily. Overall, the drug is well-tolerated. The most common toxicities of crizotinib include visual disturbances (photophobia, floaters, blurry vision), edema, and diarrhea. The most frequent grade 3/4 toxicities are elevated aminotransferases and neutropenia. With regard to these adverse events, most instances of elevated aminotransferases were asymptomatic and resolved with dose interruption or reduction. There were no episodes of febrile neutropenia. There was one grade 5 adverse event in the PROFILE 1014 trial, which was attributed to crizotinib-associated pneumonitis.

Pneumonitis/interstitial lung disease of any grade is seen in approximately 2.5% of patients treated with crizotinib [19].

3.1.1 Resistance to Crizotinib—The mPFS for patients on crizotinib for *ALK*-rearranged NSCLC is about 8–11 months based on PROFILE 1007 and PROFILE 1014. Mechanisms of resistance to crizotinib can be divided into three categories: (1) development of secondary resistance mutation in the *ALK* kinase domain leading to steric hindrance of crizotinib binding or amplification of the *ALK* gene; (2) activation of alternative bypass pathways that liberate tumoral reliance on *ALK* signaling; and (3) limited penetration into sanctuary sites, in particular the central nervous system (CNS) [20]. In one review, about 38% of patients had either a secondary mutation or amplification of the *ALK* locus; the most common point mutations being L1196M and G1269A [21]. Bypass tract activation include *EGFR* mutations, *MET* amplification, and *KRAS* mutations. However, the exact mechanism of resistance is still unknown in a large proportion of patients.

The most common site of disease progression while on crizotinib is the CNS. In a retrospective review of two clinical trials, 72% of patients who had previously treated brain metastases had secondary progression of CNS disease while on crizotinib. In patients who did not have evidence of brain metastases at baseline, 20% developed brain metastases while on therapy [22]. This observation can be partly explained by limited penetration of crizotinib into the cerebrospinal fluid (CSF) (blood–brain barrier) as suggested by Costa et al. who showed in a patient with intracranial progression on crizotinib that the CSF concentration of the drug was nearly 1000 times lower than the plasma concentration [23].

3.2 Next-Generation ALK Inhibitors in the Post-Crizotinib Setting

Given the inevitable progression of disease while on crizotinib, next-generation ALK inhibitors have been developed to overcome crizotinib resistance. There are currently three second-generation ALK inhibitors, ceritinib, alectinib, and brigatinib, that are FDA approved for use in *ALK*-rearranged NSCLC following progression on or intolerance to crizotinib. All of these drugs are more potent inhibitors of ALK than crizotinib in the pre-clinical setting. Table 1 provides a summary of the studies with these agents in the post-crizotinib setting. Active trials are ongoing with lorlatinib, a third-generation ALK inhibitor, as well as the ALK inhibitors entrectinib and ensartinib.

3.2.1 Ceritinib—The initial phase I trial (ASCEND-1) of ceritinib showed a response rate of 56% in NSCLC patients who were previously treated with crizotinib [28]; response in CNS lesions were also seen. The ASCEND-2 trial specifically examined intracranial response along with whole-body response in patients who had previously received platinum chemotherapy and crizotinib. The overall response rate (ORR) in patients with baseline brain metastases was 33%, with a disease control rate (DCR) of 74% [29]. The most common adverse events associated with ceritinib include nausea, vomiting, diarrhea, as well as rise in liver function tests, which required dose adjustment/treatment interruption in 80% of patients. The FDA-approved dosing for ceritinib is 750 mg orally daily, which is the same in the EU and Japan.

3.2.2 Alectinib—A phase I/II study of alectinib in previously crizotinib-treated patients showed a response rate of 55% with an intracranial response rate of 52%, which included a patient with leptomeningeal carcinomatosis [30]. In a single-group, multicenter phase II study conducted in the USA and Canada, the ORR was 52% with a median duration of 13.5 months [25]. Furthermore, 75% of patients with measurable CNS metastases achieved a response with a median duration of 11.1 months. Ou et al. conducted a global phase II study with alectinib, which yielded similar results, showing an ORR of 50% with a median duration of response of 11.2 months [26]. Of the patients with baseline CNS metastases, 57% achieved a response with a median duration of 10.3 months. Alectinib was overall well-tolerated with the most common adverse effects of constipation, fatigue, and myalgia occurring in approximately 30% of patients and all being grade 1 or 2. The approved dosing for alectinib in the USA and EU is 600 mg orally twice daily. The approved dose in Japan, however, is 300 mg orally twice daily. In studies conducted in Japan, dose escalation beyond 300 mg twice daily was not carried out due to limitations in Japan on the quantity of an additive present in alectinib capsules [31].

3.2.3 Brigatinib—Preclinical work showed that brigatinib was more potent and maintained activity against 17 secondary *ALK* mutations, with superior inhibitory activity compared to crizotinib, ceritinib, and alectinib [32]. The phase I/II trial showed an ORR of 72% in previously crizotinib-treated *ALK*-rearranged NSCLC patients with an intracranial response rate of 53% [33]. Updated data presented at the 2016 World Conference on Lung Cancer (WCLC) showed a mPFS of 13.4 months in crizotinib-refractory patients, which is longer than for ceritinib and alectinib in this setting [34]. An AE unique to brigatinib is early pulmonary events, including cough, dyspnea, pneumonia/pneumonitis, and hypoxia, which occurred in 6–8% of patients [33, 35] with onset typically within 7 days after initiation of brigatinib therapy. The phase II ALTA trial therefore looked at two different dosing schedules at either 90 mg daily (group A) or 90 mg daily with escalation to 180 mg daily after 7 days (group B). The ORR was 45% in group A and 54% in group B [27]. The median duration of response was 13.8 months in group A and 11.1 months in group B. Furthermore, the intracranial response was also robust at 42% in group A and 67% in group B. The cumulative incidence of early pulmonary AEs was 6%, occurring at 90 mg daily in both groups, without any occurrence after successful escalation to the 180 mg dose. The pulmonary AEs were managed with dose reduction. The FDA therefore approved brigatinib dosing as per group B in the ALTA trial. Brigatinib has not yet been approved in the EU or Japan.

3.2.4 Lorlatinib—Lorlatinib is the only third-generation *ALK* inhibitor. Preclinical data shows that it is more potent than crizotinib, ceritinib, and alectinib with in vivo activity against the highly resistant *G1202R* mutation, which is resistant to the other TKIs, including brigatinib [36]. At the 2017 American Society for Clinical Oncology (ASCO) meeting, Shaw et al. presented the preliminary data for the phase I/II trial of lorlatinib in *ALK*-positive patients who had received one or more prior *ALK* TKI. Lorlatinib demonstrated impressive activity in heavily pretreated patients; the relative risk (RR) ranged from 31% in patients who received three prior TKIs with or without chemotherapy to 57% in patients who only received previous crizotinib [37]. The intracranial RR also ranged from 43% to

60%, with an overall RR of 48.1%. Lorlatinib appeared to be well-tolerated with the most significant treatment-related AEs being hypercholesterolemia and hypertriglyceridemia. Only 3.4% of patients discontinued treatment due to AEs. AEs unique to lorlatinib are cognitive defects (19% of patients) and mood effects (13% of patients). According to the investigators, the majority were grade 1 and were transient/reversible.

3.2.5 Entrectinib and Ensartinib—Entrectinib is an oral inhibitor of *TRK A/B/C*, *ROS1*, and *ALK*. The results of two phase I studies with 119 patients have been published, with 71 of these patients having NSCLC [38]. No responses were observed in patients who had previously received an ALK TKI. The ORR was 57% in *ALK*-rearranged solid tumors, which included NSCLC.

Ensartinib is an oral inhibitor of *ALK* with activity also against *MET*, *ABL*, *ROS1*, *Axl*, *EPHA2*, *LTK*, and *SLK*. The results of the phase I/II study with ensartinib in patients with NSCLC that were either TKI-naïve or resistant to crizotinib were presented at the IASLC 2016 conference [39]. Responses were seen in patients who are crizotinib naïve (77%) and crizotinib resistant (73%).

3.3 Next-Generation ALK Inhibitors as First-Line Therapy

As progression on crizotinib eventually occurs, particularly in the CNS, there is great interest in understanding whether the initiation of second-generation ALK inhibitors as first-line therapy is a superior treatment paradigm.

3.3.1 Ceritinib—The phase III ASCEND-4 trial demonstrated the superiority of ceritinib as first-line therapy for *ALK*-rearranged NSCLC over platinum–pemetrexed doublet, including improved ORR in the CNS of 72.7% compared to 27.3% [40]. The mPFS as assessed by an independent committee was 16.6 months for ceritinib and 8.1 months for chemotherapy with a HR of 0.55 ($p < 0.00001$). The efficacy appeared to differ based on the presence of brain metastases at baseline. The mPFS in patients without baseline brain metastases was 26.3 months for ceritinib compared to 8.3 months for chemotherapy (HR 0.48). In contrast, in patients with baseline brain metastases, the mPFS was 10.7 months for ceritinib and 6.7 months for chemotherapy (HR 0.70). Ceritinib was approved in May 2017 for the front-line treatment of *ALK*-positive NSCLC but has not been compared head-to-head against crizotinib in the front-line setting. Looking at two different trials, in patients that progressed on crizotinib who then were switched to ceritinib therapy, the combined mPFS was 17.4 months [41] compared to 16.6 months with ceritinib alone [40].

In the ASCEND-5 phase III trial, ceritinib was compared to chemotherapy in patients with disease progression after one to two lines of chemotherapy and crizotinib. The response rate for the ceritinib group was 39.1% compared to 6.9% in the chemotherapy group [24]. While the FDA-approved dose of ceritinib is 750 mg orally daily, 80% of patients in the ASCEND-5 trial required dose adjustment, interruption, or delay, with 61% requiring at least one dose reduction. The most common adverse symptoms that led to dose reduction include nausea, vomiting, and diarrhea. Given the concern regarding poor tolerance of ceritinib, the ASCEND-8 trial sought to evaluate whether lower doses of ceritinib at 450 mg and 600 mg given with a low-fat meal could reduce the adverse gastrointestinal effects of

ceritinib 750 mg taken on an empty stomach. Ceritinib 450 mg taken with a low-fat meal demonstrated similar pharmacokinetics as 750 mg fasting, with less gastrointestinal (GI) adverse effects and no grade 3 GI events [42]. However, the overall rate of suspected drug-related adverse events occurred in 41% of patients at the 450 mg dose and no efficacy data with this dose is as yet available. These data suggest that modification of the approved dose may allow greater tolerability of the drug.

3.3.2 Alectinib—The preliminary results of the phase III J-ALEX trial comparing upfront alectinib versus crizotinib in treatment-naïve patients with *ALK* NSCLC were presented at ASCO 2016; there was a significantly increased mPFS favoring alectinib over crizotinib (HR 0.34, $p < 0.0001$) [43]. This study was updated at ASCO 2017 and immediately published thereafter. The mPFS was not assessable on alectinib compared to 10.2 months on crizotinib [44]. Response rate also favored alectinib at 85% compared to 70% with crizotinib. However, as the study was conducted exclusively in Japan, the practice was not widely adapted given concerns regarding applicability with respect to the patient population and different dosage used at 300 mg orally twice daily. At ASCO 2017, Shaw et al. reported results of the phase III global ALEX trial, which was subsequently published. In this study, the dosage of alectinib was 600 mg orally twice daily. Alectinib led to a significant reduction in risk of progression/death with HR 0.47 ($p < 0.0001$); the mPFS for crizotinib was 11.1 months, but had not yet been reached for alectinib [45, 46]. The intracranial response for patients with measurable CNS lesions at baseline was 50% for crizotinib and 81% for alectinib; the time to progression in the CNS also favored alectinib with a HR of 0.16 ($p < 0.0001$). Grade 3/4 AEs were also less frequent with alectinib than with crizotinib (41% vs. 50%, respectively). While the FDA has not yet approved alectinib as front-line therapy for patients with *ALK*-positive NSCLC, the results of the J-ALEX and ALEX trials suggest that front-line treatment with alectinib leads to a significantly longer PFS than crizotinib and appears to be better tolerated. The results of the two trials also suggest that front-line alectinib does not have an inferior PFS compared to sequential crizotinib followed by alectinib. Table 2 summarizes current data on *ALK* inhibitors used in the front-line setting.

3.4 Sequence of *ALK* Inhibitors

While it is not yet known which *ALK* inhibitor is the ideal first-line therapy, there are more data to guide selection of the next-generation *ALK* inhibitor post-crizotinib. As ceritinib was only recently approved as initial therapy, there is little data regarding front-line progression on this drug. With advancements in sequencing technology, multiple mutations in *ALK* have been discovered that convey either resistance or sensitivity. The mutation profile coverage varies among the next-generation *ALK* inhibitors [47]. Currently, knowing the resistance mutation does not impact the choice of postcrizotinib therapy, especially as mutations account for only one-third of resistance mechanisms. But, given the availability of several next-generation *ALK* inhibitors, the presence of a specific resistance mutation, as well as the cost and adverse effect profile of each drug, can help guide therapy.

Gainor et al. evaluated post-progression biopsies of patients treated with second-generation *ALK* inhibitors and found that *ALK* resistance mutations were present in 56% of patients who progressed on second-generation *ALK* TKIs (compared to 20% of patients who

progressed on crizotinib), with the most common being the *G1202R* mutation [47]. They proposed that in the setting of progression on a second-generation *ALK* inhibitor, repeat biopsy to assess for *ALK* mutations should be strongly considered as the presence of an *ALK* resistance mutation suggests that it remains the main oncogenic driver and the patient should be considered for further *ALK*-directed therapy. However, should the tumors not harbor *ALK* mutations, then other treatment strategies (i.e., combination chemotherapy) should be considered over *ALK* TKI monotherapy [8]. The data generated by Gainor et al. is in patients who received next-generation *ALK* inhibitors after having received crizotinib. It is currently not known if the profile of resistance mechanisms in patients who receive these agents as front-line therapy will be the same.

The *L1198F* mutation is worthy of further discussion as it conveys sensitivity to crizotinib but not likely to any of the other next-generation *ALK* inhibitors. This was first presented by Shaw et al., who described a patient with metastatic *ALK*-rearranged NSCLC who received lorlatinib through a clinical trial after progression of disease on crizotinib, ceritinib, and carboplatin–pemetrexed chemotherapy [48]. At time of progression on lorlatinib, she underwent biopsy of a resistant liver lesion which demonstrated the presence of *C1156Y* (previously detected) and *L1198F* mutations. Pharmacodynamic studies revealed increased binding affinity to crizotinib of this specific mutation compared to other *ALK* inhibitors. The patient was re-challenged with crizotinib and exhibited a significant radiographic response. This case report demonstrates the role for evaluating resistance mutations at time of progression, particularly in patients who have had two or more *ALK* inhibitors.

4 Post-*ALK* Inhibitor Therapy

There has not been any data published on the efficacy of chemotherapy for patients with *ALK*-rearranged NSCLC after progression on two or more *ALK* inhibitors. The phase III trials of ceritinib and crizotinib showed response rates of 27–45% to chemotherapy in patients with *ALK*-rearranged NSCLC. In a large retrospective study, however, the RR to platinum-based chemotherapy was shown to be only 18% in treatment-naïve *ALK*-rearranged patients [49]. The results of the ASCEND-5 trial showed that the response rate to ceritinib was significantly better than to chemotherapy as second-line therapy (39.1% vs. 6.9%) [41]. In this study, however, the patients received second-line single agent docetaxel or pemetrexed as they had all previously received front-line platinum-based chemotherapy. An earlier retrospective review by Shaw et al. showed that in comparison to *ALK*-negative patients, *ALK*-positive patients had a similar improved mPFS when treated with a platinum–pemetrexed doublet [50]. While the efficacy of the platinum–pemetrexed doublet in *ALK* TKI-refractory patients who are chemotherapy-naïve has not been explicitly reported, existing data suggest that it is a combination that is worthy of consideration.

The PD-1 (programmed cell death-1) inhibitors nivolumab and pembrolizumab as well as the PD-L1 (programmed cell death ligand-1) inhibitor atezolizumab are all approved for the treatment of advanced NSCLC after large trials demonstrated their superiority to docetaxel chemotherapy in patients that have progressed on standard platinum-based doublet chemotherapy [51–54]. Pembrolizumab has also been approved as initial therapy for patients with metastatic NSCLC with PDL1 expression ≥ 50% as evaluated by IHC [55] or in

conjunction with carboplatin and pemetrexed as first-line therapy for all non-squamous histologies irrespective of PD-L1 expression [58]. While PD-L1 expression is not an absolute indicator of response to checkpoint inhibition, there are data to suggest that increased PD-L1 is associated with improved response to these agents [56].

Preclinical data suggested that *ALK*-rearranged and *EGFR*-mutant NSCLC cells had significantly higher PD-L1 expression than their wild-type counterparts, suggesting that they may be responsive to checkpoint inhibitors [57]. However, preclinical data also showed that *EGFR* TKIs such as gefitinib decreased PD-L1 expression [58]. Therefore, one mechanism of 'resistance' to checkpoint inhibitors in TKI-refractory tumors could be through the down-regulation of PD-L1 expression by the TKI. Gainor et al. conducted a retrospective review on *EGFR*-mutated and *ALK*-rearranged NSCLC patients treated with PD-1/PD-L1 inhibitors after progression on TKIs. Though their sample size was small, zero of six patients with *ALK*-rearranged NSCLC had an objective radiographic response to checkpoint inhibition [59]. They also assessed PD-L1 expression in *ALK*-rearranged NSCLC prior to crizotinib and at the time of crizotinib resistance. They found that 47% of crizotinib-naïve patients had PD-L1 $\geq 5\%$ and 25% of crizotinib-resistant patients had PD-L1 $\geq 5\%$. Recently, Garassino et al. presented the results from the ATLANTIC study that included a cohort of *EGFR*- and *ALK*-positive patients treated with durvalumab, a PD-L1-directed antibody [60]. All patients had received at least two prior treatments, including a TKI and platinum-based chemotherapy. The response rate observed was 12.2% in patients whose tumors had high PD-L1 expression ($n = 74$) and 3.6% in patients who had low or negative PD-L1-expressing tumors ($n = 28$). The mPFS was 1.9 months in all patients, with a median survival ranging from 9.9 to 13.3 months.

Lack of activity of PD-1/PD-L1-directed agents has also been observed in patients who are never smokers and in patients with *EGFR* mutation-positive NSCLC [51, 52, 61]. It has been shown that NSCLC patients with tumors that have a high mutational burden have a greater probability of benefit from checkpoint inhibition [62]. It is hypothesized that tumors with high mutational burden express more novel neoantigens that can be targeted by an activated immune system, whereas tumors with low mutational burden may express far fewer neoantigens, limiting the anti-tumor efficacy of the immune system. It is well-recognized that tumors in never smokers and *ALK*-positive and *EGFR*-mutated NSCLC patients have low mutational burden. This observation may also help to explain the limited efficacy of checkpoint inhibitors in these patients.

While there are no trials comparing immunotherapy with *ALK* TKIs as upfront treatment of *ALK*-rearranged NSCLC, the data at least suggest that PD-1/PD-L1 inhibitors are not effective in a high proportion of *ALK*-positive patients who have progressed on TKI therapy. It is unclear if combination immune therapy such as combination of an anti-CTLA4 (cytotoxic T lymphocyte-associated molecule-4) and anti-PD-1/PDL1 antibodies or combination of PD-1-directed agents with chemotherapy will provide greater benefit in these patients.

5 Localized Therapy for Brain Metastases

While next-generation ALK TKIs can delay intracranial progression, it eventually does occur and therefore it is important to consider other localized therapy for the treatment of brain metastases, including radiation and surgery. Maximum preservation of cognitive function must be considered, especially as patients with *ALK*-rearranged NSCLC tend to be younger. Stereotactic radiosurgery (SRS) is recommended if there are a few discrete lesions, but whole brain radiation (WBRT) must be considered for greater burden of disease. It is currently unknown if concurrent administration of radiation while on an *ALK* TKI is safe and therefore it has been accepted practice to have patients suspend taking the drug during radiation treatment [63]. Mak et al. assessed the impact of genetic alterations on survival after receiving radiation therapy for brain metastases in NSCLC. They found a significantly improved OS of 26.3 months for patients with *ALK*-rearranged NSCLC compared with 5.5 months for patients without any identifiable genetic alterations ($p = 0.001$) [64]. It is thought that radiation can increase the permeability of the blood–brain barrier, thereby rendering TKI more effective. One retrospective study showed that patients with only intracranial progression had a continued mPFS of 7.1 months when resumed on crizotinib post-radiation [65]. While it is generally recommended to continue the same TKI post-radiation, the benefit of switching TKI at that time has not been specifically addressed.

6 Future Directions

The development and approval of the next-generation ALK inhibitors have improved the options for patients with *ALK*-rearranged NSCLC. Crizotinib was the first FDA-approved agent for initial therapy of *ALK*-rearranged NSCLC. However, the results of the J-ALEX, ALEX, and ASCEND-4 trials suggest that patients derive greater clinical benefits by starting on next-generation ALK inhibitors compared to crizotinib, leading to the recent approval of ceritinib as initial therapy. We also expect that alectinib will soon receive the same approval. With the approval of a second-generation ALK inhibitor as initial therapy, it is unclear if the patient would be a candidate for an alternative second-generation inhibitor at progression. The different mutation profiles suggest that switching between second-generation inhibitors may be a possible therapeutic option, but it is not known if the same resistance mutations will develop. Further investigation is therefore needed to better understand the mechanisms that drive the development of resistance in patients who start on the next generation of ALK inhibitors.

The optimal treatment for TKI-resistant *ALK*-rearranged NSCLC is also unclear. While the data for either platinum-based chemotherapy or immunotherapy does not appear to be favorable, prospective data are needed. A strategy that should be considered is combination therapy with other agents, as most of the work in overcoming *ALK* resistance thus far has focused on monotherapy with more potent next-generation ALK inhibitors. Combining an *ALK* TKI with a second TKI that targets bypass tracts (i.e., EGFR, cKIT, MEK) could be a viable strategy in tumors where the resistance pathway has been identified [66]. While checkpoint inhibitors as monotherapy does not seem to be efficacious, the combination should be examined given pre-clinical data suggesting the upregulation of PD-L1 expression by TKIs, which if used in combination with a checkpoint inhibitor may result in greater

response. This approach has been attempted in *EGFR*-mutated NSCLC with the combination of osimertinib (EGFR TKI) and durvalumab (PD-L1 inhibitor), but the trial was discontinued due to an increased incidence of pneumonitis [66]. It is not known whether the same adverse effects would be observed with the combination of an ALK TKI and a checkpoint inhibitor.

7 Summary

From the discovery of the *ALK-EML4* fusion as an oncogenic driver in a subset of NSCLC one decade ago to today, significant advancements have been made in the treatment of patients with *ALK*-rearranged NSCLC. With the arrival of next-generation ALK inhibitors, some of which have moved into the front line as initial therapy, patients have been able to derive greater clinical benefit. However, there is a significant need to understand the drivers of and mechanisms underlying resistance as it inevitably occurs in patients treated with TKIs. The development of novel agents that target other oncogenic pathways raises the possibility for combination therapy or salvage therapy for TKI-refractory patients. The progress that has been made in the treatment of *ALK*-rearranged NSCLC highlights the importance of understanding molecular drivers of cancer as we enter the era of precision oncology.

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Key Points

New ALK specific agents have changed the treatment options for ALK non-small cell lung cancer.

Studies have shown that these new agents may be more effective than crizotinib as first-line treatment.

Active research is ongoing regarding the appropriate sequence of therapy especially for refractory disease.

Second-generation anaplastic lymphoma kinase (ALK) inhibitors in the post-crizotinib setting

Table 1

Drug	Trial phase	ORR (%)	Intracranial RR (measurable disease at baseline) (%)	mPFS (months)	Common AEs (>20%)	Dosing (all PO)
Ceritinib	III [24]	39.1	35	5.4	Diarrhea (68%), nausea (58%), vomiting (44%), decreased appetite (40%), weight loss (27%), transaminitis (23%)	750 mg daily
Alectinib	II [25, 26]	48–50	57–75	8.1–8.9	Constipation (30%), fatigue (30%), peripheral edema (25%), myalgia (23%)	600 mg bid
Brigatinib ^a	II [27]	54	67	12.9	Nausea (40%), diarrhea (38%), cough (34%), headache (27%), fatigue (27%), vomiting (23%)	90 mg daily × 7 days followed by 180 mg daily

AEs: adverse events, *bid* twice daily, *FDA* Food and Drug Administration, *mPFS* median progression-free survival, *ORR* overall response rate, *RR* relative risk

^aResponse based on the US FDA-approved dose; the trial tested two different dosing schema

Efficacy of anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitors (TKIs) as front-line therapy

Table 2

Drug	ORR (%)	Intracranial RR (measurable disease at baseline)	mPFS (months)	Common AEs (>20%)	Dosing
Crizotinib [18]	74	18% [22] ^a	10.9	Visual disturbances (71%), diarrhea (61%), edema (49%), vomiting (46%), constipation (43%), transaminitis (36%), abdominal pain (26%), dysgeusia (26%), headache (22%)	250 mg PO BID
Ceritinib [40]	72.5	72.7%	16.6	Diarrhea (85%), nausea (69%), vomiting (66%), transaminitis (55%), abdominal pain (25%)	750 mg PO daily
Alectinib [44, 46]	85 (J-ALEX) 82.9 (ALEX)	81% (ALEX)	NE (J-ALEX) 25.7 (ALEX) ^b	Constipation (35%) ^c	300 mg PO BID (J-ALEX) 600 mg PO BID (ALEX)

AEs: adverse events, *BID* twice daily, *mPFS* median progression-free survival, *NE* not estimable, *ORR* overall response rate, *PO* orally, *RR* relative risk

^aFrom a retrospective review of PROFILE 1005 and PROFILE 1007; not reported in PROFILE 1014

^b25.7 months as assessed by an independent review committee, not reached as assessed by investigators

^cReported in J-ALEX only