How I treat ALK-positive non-small cell lung cancer

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ABSTRACT
Since the discovery of anaplastic lymphocyte kinase (ALK) rearrangement in non-small cell lung cancer (NSCLC) and subsequent development of increasingly effective and central nervous system (CNS)-penetrant first-generation, second-generation and third-generation ALK tyrosine kinase inhibitors (TKIs), the landscape of resistance mechanisms and treatment decisions has become increasingly complex. Tissue and/or plasma-based molecular tests can identify not only the rearrangement proper but also common resistance mechanisms to guide decision-making for further lines of treatment. However, frequently encountered questions exist regarding how to diagnose ALK rearrangement, how to select a first-line ALK TKI, how to diagnose and manage ALK TKI resistance, how to control CNS disease and how to handle failure of ALK inhibition. Herein, we attempt to answer these questions through the evidence-based interpretation of studies on ALK-rearranged NSCLC combined with experience gained from our institution. The authors also propose a therapeutic algorithm for the management of this complex and highly treatable disease to assist clinicians globally in the treatment of patients with ALK-positive NSCLC.

INTRODUCTION
Rearrangements in the gene encoding anaplastic lymphocyte kinase (ALK) are found in 3%–5% of patients with non-small cell lung cancer (NSCLC).1 Ever-expanding assays, such as high-throughput sequencing of tissue samples2 and cell-free DNA (cfDNA) from peripheral blood sample,3 can detect ALK rearrangements and resistance mechanisms for use of highly potent tyrosine kinase inhibitors (TKIs). Since the introduction of the first-generation ALK TKI crizotinib, more selective and higher central nervous system (CNS)-penetrant second-generation (ceritinib, alectinib and brigatinib) and third-generation (lorlatinib)4 ALK TKIs are in use and others are in development (ie, ensartinib). Now, molecular analysis has revealed why treatment of easily identifiable and highly TKI-sensitive ALK rearrangements has remained a clinical challenge.

HOW I DIAGNOSE ALK REARRANGEMENT
Different methodologies are used for tissue-based ALK rearrangement detection as either fusion events (fluorescence in situ hybridisation) or fusion protein expression (immunohistochemistry, IHC) as recommended by International Association for the Study of Lung Cancer (IASLC)/College of American Pathology (CAP) guidelines.2 The addition of hybrid capture-based next-generation sequencing (NGS) to these techniques can overcome the limits of multiple single-gene tests, has similar performance to IHC5 and can identify ALK-acquired resistance mutations outside of gene fusions. Plasma-based cfDNA techniques or ‘liquid biopsy’ for detecting ALK mutations now offer a rapid, minimally invasive and highly specific diagnosis.3 At the 2019 American Association for Cancer Research Annual Meeting, the results of the NILE trial demonstrated that cfDNA detects all guideline 7 (G7) biomarkers (epidermal growth factor receptor (EGFR), ALK, C-ros oncogene 1 (ROS1), v-raf murine sarcoma viral oncogene homolog B1 (BRAF), Rearranged during Transfection (RET), hepatocyte growth factor receptor (MET) and, human epidermal growth factor receptor 2 (ERBB2)) included in IASLC/CAP guidelines at a rate similar to a tissue-based assay. Further, 30.2% of patients who had insufficient tissue for analysis were incompletely genotyped, or were negative for tissue biomarkers were able to obtain a cell-free genotyping result. Positive predictive value of cfDNA for tissue genotyping for G7 biomarkers was 100%.6

We consider the use of a liquid biopsy at the time of initial diagnosis in patients who require molecular analysis, particularly when tissue is scarce, significant delays in diagnosis are expected or contraindications to the biopsy exist. As stated by the IASLC liquid biopsy statement paper, a positive diagnosis of ALK rearrangement by a liquid biopsy is sufficient to initiate ALK-targeted therapy.3

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HOW I TREAT ALK REARRANGED NSCLC IN THE FIRST-LINE

Second-generation ALK TKIs are now the first-line treatment of advanced ALK-positive NSCLC. Crizotinib still remains the standard of care first-line treatment in several regions of the world due to the efficacy demonstrated in the randomised phase III PROFILE 1014 trial when compared with platinum-based chemotherapy, in terms of both overall response rate (ORR; 74% vs 45%; p<0.001) and progression-free survival (PFS, 10.9 vs 7.0 months; HR, 0.45; p<0.001). In the USA, alectinib and ceritinib are now the first-line treatments for advanced ALK-positive NSCLC according to the Food and Drug Administration approval. In the head-to-head comparative ALEX trial, alectinib was shown to be superior to crizotinib in terms of ORR (82.9% vs 75.5%, p=0.09), PFS (34.8 vs 10.9 months; HR, 0.43) and toxicity profile (adverse events (AE) grade 3–5; 44.7% vs 51.0%).

PFS is much longer with upfront use of alectinib than the cumulative PFS achievable with the sequential use of ALK TKIs and is associated with a significant reduction in the cumulative incidence of brain metastases when compared with crizotinib. Ceritinib showed superiority to standard of care platinum-pemetrexed chemotherapy in the phase III ASCEND-4 trial (ORR, 72.5% vs 26.7%; PFS, 16.6 vs 8.1 months). This agent also demonstrates important intracranial and extracranial activity. Unfortunately, the toxicity profile of ceritinib can limit its clinical utility. In the pivotal randomised trial, the prevalence of dose adjustments or interruptions was 80% in the ceritinib arm compared with 45% in the chemotherapy arm, respectively. However, in the ASCEND-8 trial, a dose adjustment was proposed with food interaction mainly in order to reduce gastrointestinal toxicity, concluding that 450 mg taken with food has similar drug exposure and activity to 750 mg administered under fasting conditions.

Within our institution, alectinib is first-line ALK TKI due to its PFS advantage, brain metastasis cumulative incidence reduction and favourable toxicity profile. Regarding other second-generation ALK TKIs, brigatinib showed superiority to crizotinib in the phase III ALTA-1L trial (estimated 12 month PFS, 67% vs 43%; HR, 0.49; p<0.001) (table 1). All these drugs, including the third-generation ALK inhibitor lorlatinib, have demonstrated activity in the CNS. It is important to note that no randomised trials have compared alectinib with the other second-generation or third-generation ALK TKIs.

HOW I TREAT ALK RESISTANCE

ALK resistance involving mutations or gene amplifications (ALK-dependent) and alternative signalling pathways (ALK-independent) are important to identify in clinical practice as most patients with the initial response to ALK TKI relapse within 1 to 2 years, and approximately 50% of patients will have CNS disease during the course of treatment. ALK-dependent mechanisms involve mutations in the kinase domain and only approximately 20% of patients develop ALK-acquired resistance mutations after treatment with crizotinib. The ‘gatekeeper mutation’ L1196M is analogous to the T790M EGFR mutation and is perhaps the most well-known resistance mechanism. Importantly, the G1202R substitution that confers resistance to all second-generation ALK TKIs is found in only approximately 2% of crizotinib-resistant patients; most frequently after treatment with a second-generation ALK TKI (21%–43%).

Fortunately, after progression on a second-generation ALK TKI, emerging data from studies of the third-generation ALK inhibitor lorlatinib have shown promise. Lorlatinib demonstrates high potency regardless of the resistance mechanism and against several ALK-dependent resistance mechanisms including L1196M and G1202R substitutions. In a phase II trial of patients with ALK-positive NSCLC treated with lorlatinib, patients previously treated with crizotinib had an ORR of 69% and median PFS was not reached. The most common treatment-related AEs of any grade were hypercholesterolaemia (81%) and hypertriglyceridaemia (60%) with grade 3–4 events in 16% of patients for each outcome. Importantly, among patients who progressed on two or more ALK TKIs (including ceritinib and alectinib), ORR was 39% and median PFS was 6.9 months. In a subsequent analysis of tissue and plasma genotyping, ORR for patients with detectable ALK mutations in the plasma (73%) or tissue (73%) was not significantly different from patients without detectable mutations in the plasma (75%) or tissue (74%). Those with mutations in the plasma (62%) or tissue (69%) displayed higher responses to lorlatinib than those without mutations in the plasma (32%) or tissue (7%). The activity of brigatinib in alectinib-refractory patients is limited with a reported ORR of 17% in a recent multicentre study, suggesting that a change to brigatinib may have little clinical utility.

These results demonstrate that most crizotinib-resistant tumours are still driven by ALK and are sensitive to subsequent ALK TKI therapy. However, patients treated with second-generation ALK inhibitors without detectable ALK mutations in the plasma or tissue respond less well to subsequent-generation ALK TKIs and may signify development of an ALK-independent resistance mechanism.

ALK-independent mechanisms rely on activation of alternative signalling pathway, epithelial-to-mesenchymal transition (EMT) or change in tumour histology. Resistance to ALK inhibition can develop through activation of parallel or downstream signalling pathways. In a study assessing resistance mechanisms to crizotinib, only 28% of cases of resistance were due to genetic alterations in the drug target. Proposed ALK-independent mechanisms of resistance include alteration in EGFR, mast/ stem cell growth factor receptor (KIT) and insulin-like growth factor 1 receptor, and activation of phosphorylation-dependent signalling pathways.

In an analysis of three patients resistant to crizotinib without ALK-resistance mutations, enrichment of nine genes in four EMT pathways were identified. Additionally, transformation to small cell lung cancer has been described as a
Table 1  Randomised phase III trials evaluating ALK TKIs as first-line treatment for advanced/metastatic ALK-rearranged NSCLC

| Trial     | n  | ALK detection method | Treatment arms | Median follow-up (mos) | ORR (%) | PFS (mos) (95% CI) | HR (95% CI) | Log rank p value | OS (mos) (95% CI) | HR (95% CI) | Log rank p value |
|-----------|----|----------------------|----------------|------------------------|---------|-------------------|-------------|------------------|------------------|-------------|------------------|
| PROFILE 1014 | 172 | FISH*                | Crizotinib 250 mg twice daily vs Platinum-Pem x 6 | 45.7 mos vs 45.5 mos | 75† vs 70 (6.8–8.2)† | 0.45 (0.35–0.60) | p<0.001 vs 47.5 (32.2–NR) | 0.76 (0.548–0.053) | p=0.978 |
| ASCEND 4   | 189 | IHC*                 | Ceritinib 750 mg/d vs Platinum-Pem x 4Pem | 19.7 mos vs 26.7† mos | 72.5† vs 8.1 (5.8–11.1)† | 0.55 (0.42–0.73) | p<0.0001 vs 26.2 (22.8–NR) | 0.73 (0.50–1.08) | p=0.056 |
| J-ALEX     | 103 | IHC, FISH or RT-PCR* | Alectinib 300 mg twice daily vs Crizotinib 250 mg twice daily | 20.5 mos vs 20.4 mos | 92† vs 79† | 25.9 (20.3-NR)† vs 10.2 (8.3–12.0)† | 0.38 (0.26–0.55) | p<0.0001 – – – | – – – |
| ALEX       | 152 | IHC*                 | Alectinib 600 mg twice daily vs Crizotinib 250 mg twice daily | 27.8 mos vs 22.8 mos | 82.9† vs 98.5† | 34.8 (17.7-NR)† vs 10.9 (9.1–12.9)† | 0.43 (0.32–0.58) | – vs NR | 0.76 (0.50–1.15) |
| ALTA-1L    | 137 | Local ALK testing    | Brigatinib 180 mg/d vs Crizotinib 250 mg twice daily | 11.0 mos vs 9.3 mos | 71† vs 9.8 (9.0–12.9)† | 0.49 (0.33–0.74) | p=0.0007 – – – | – – – |

*Independent central review.
†Investigator-assessed.
‡Included patients who had received platinum-based chemotherapy as first-line therapy.
§Preceded by a lead-in phase of 7 days at 80 mg/d.
* Determined centrally.
ALK, anaplastic lymphoma kinase; BID, twice daily; FISH, fluorescence in situ hybridisation; IHC, immunohistochemistry; NR, not reached; NSCLC, non-small cell lung cancer; ORR, overall response rate; PFS, progression-free survival; Pem, pemetrexed; mos, months.
Detection of these poorly understood bypass mechanisms is a clinical challenge and future studies to investigate combination treatments in ALK-resistant NSCLC are needed. It is important to be aware that patients who progress while on ALK TKI and who do not have a resistant mechanism identified constitute an unmet medical need.

If we suspect disease progression during treatment with first-generation or second-generation ALK TKI, a liquid biopsy is our first choice for diagnosis of resistance mechanisms given the high specificity of plasma cfDNA for detection of ALK mutations, although a tissue biopsy remains a valid option. In cases of suspected small cell lung cancer transformation as a mechanism of resistance, a tissue biopsy is mandatory. A tissue biopsy should also be pursued in cases where a liquid biopsy does not reveal a likely resistance mechanism. The testing of cfDNA is preferred as it allows for detection of not only intrinsic ALK mutations but also bypass tract activation. In addition, if oligoprogression is observed, loco-regional treatment with radiation in conjunction with the continuation of current ALK TKI therapy may be considered after multidisciplinary discussion. During radiation therapy for brain metastases, ALK TKIs are usually withheld on the days of local therapy with radiation and restarted on the day after radiation is completed in order to minimise the risk of neurotoxicity. No change in dosage is required.

**How I Treat CNS Disease in ALK Rearranged NSCLC**

Metastatic CNS disease is present in approximately 20%–30% of patients with ALK-positive NSCLC at the time of diagnosis, but the incidence increases up to 50% over the course of the disease. Potential for achieving adequate CNS TKI penetration increases with the use of higher generation TKIs. Crizotinib has poor CNS penetration due to a low CSF-to-plasma concentration ratio (0.0026), explaining why the CNS is a common site of metastasis or non-target disease progression in 70% of patients with crizotinib failure. Historically, loco-regional treatments were considered the standard of care as patients with NSCLC with CNS metastases were most commonly treated with resection and/or radiotherapy (stereotactic radiosurgery (SRS) and/or wholebrain radiation therapy (WBRT)). The combination of radiation and crizotinib was shown to prolong survival in the pre-second-generation TKI era. However, alectinib, in contrast to crizotinib, is not a substrate for P-glycoprotein, which promotes efflux at the blood-brain barrier. As a result, alectinib achieves higher concentrations in the brain, demonstrated significantly prolonged CNS PFS in the phase III ALEX trial compared with crizotinib in patients either with (HR, 0.40; 95% CI 0.25 to 0.64) or without (HR, 0.51; 95% CI 0.33 to 0.80) baseline CNS disease.

The high intracranial activity of alectinib and other second-generation ALK TKIs may allow delay in the use of radiotherapy in patients with asymptomatic CNS disease on presentation. Further, mildly symptomatic patients may still be considered for treatment with second-generation ALK TKI given the expected rapidity of response if close monitoring is ensured after multidisciplinary discussion. Patients with large volume or symptomatic CNS involvement should receive loco-regional treatments (either SRS or WBRT), based on the number and dimensions of the lesions in addition to the appropriate ALK TKI.

**How I Treat Failure of ALK Inhibition**

Chemotherapy is still the backbone of NSCLC and in ALK-positive patients progressing after ALK TKIs
without actionable resistance mutations. Platinum-based chemotherapy is still a valid option for these patients. The role of single-agent immune checkpoint inhibitors (ICIs) is still a matter of debate. The combination of an ALK inhibitor and an ICI were studied and resulted in a negative outcome. For example, in the phase I/II study combination nivolumab with crizotinib as a first-line treatment (CheckMate 370), the enrollment was discontinued due to significant hepatotoxicity.\(^\text{32}\) Similar results were observed in the combination of ceritinib and nivolumab presented at the American Society of Clinical Oncology Annual Meeting in 2017. In contrast, a manageable toxicity profile has been reported with the combinations avelumab with lorlatinib in the phase 1b/2 JAVELIN Lung 101 trial\(^\text{33}\) and atezolizumab with alectinib\(^\text{34}\) with no new or unexpected side effects. Encouraging data are emerging with the chemoinmunotherapy combinations, as recently reported in a subset analysis of the IMpower 150 trial,\(^\text{35}\) although the small sample size of ALK-positive patients included in the study does not allow for definitive conclusions in outcomes.

**CONCLUSIONS**

The therapeutic landscape of ALK-rearranged NSCLCs is rapidly evolving and second-generation ALK TKIs have now become established first-line treatment (figure 1). As cfDNA and tissue NGS techniques continue to advance, we expect a better understanding of the optimal treatment sequencing to emerge. However, several questions still remain unanswered and resistance mechanisms to these agents need to be more fully understood. Crizotinib may still have a role for use in countries where second-generation ALK TKIs are not yet approved in treatment-naïve patients, although we know that the sequential use of next-generation ALK inhibitors is essential. Finally, the role of immunotherapy in combination with chemotherapy should be addressed in prospective clinical trials in order to produce more robust efficacy data in this small subgroup of NSCLC patients and to define their exact place in the therapeutic armamentarium of ALK-rearranged NSCLCs.

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