

# THE ALKFUSION REPORTER

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## Welcome to ALKFUSION

Welcome to the March edition of *The ALKFusion Reporter*. The ALKFusion founders have been busy in the past month, meeting with ALK researchers, and attending a conference on ALK (and other oncogene drivers) in Philadelphia. Follow us on Twitter and Facebook to get the latest updates!

In this month's edition, we see a theme that we've seen for a few months: lots of research on testing methods, whether NGS, IHC, or FISH, and, in particular, testing upon progression.

And did we mention that TWO promising compounds were discovered as ALK inhibitors? This is of course preliminary, but stay tuned!

Did we miss anything in this issue you think should be included? Care to volunteer your talents to a future issue of *The ALKFusion Reporter*? Have other feedback? Contact us on the *ALKFusion* Facebook

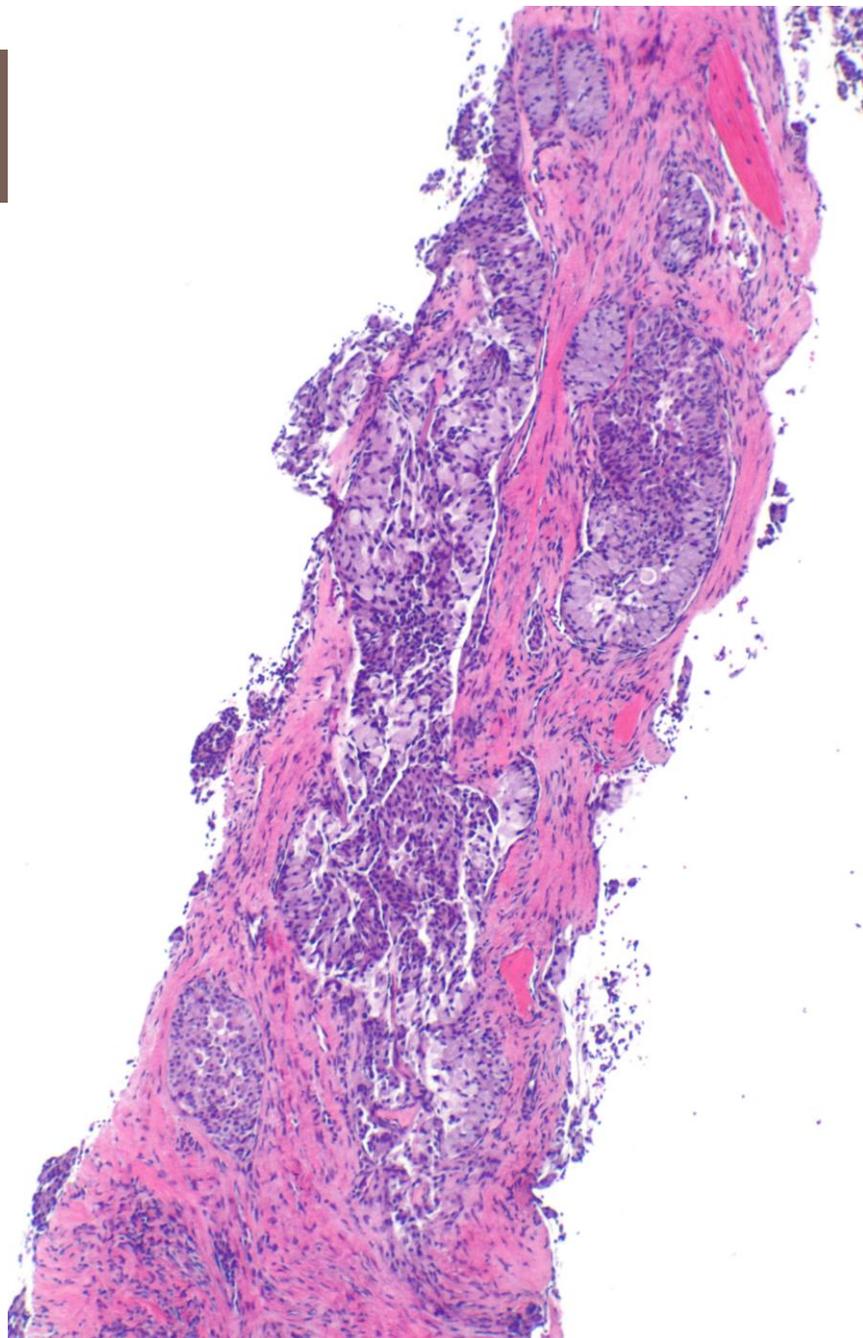
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### Comparison of ALK Detection by FISH, IHC and NGS to Predict Benefit from Crizotinib in Advanced Non-small-cell Lung Cancer

“We implemented three ALK laboratory methodologies: fluorescence in situ hybridization (FISH), immunohistochemistry (IHC) and next-generation sequencing (NGS) to detect EML4-ALK fusions and compared the predictive value for Crizotinib efficacy in ALK-positive patients....FISH present a certain false-negative rate although considered the gold standard. Ventana-D5F3 IHC is qualified as a screening tool, while NGS positive may predict clinical benefit of Crizotinib more accurately, allowing efficient test for specific variants and concurrent genomic alterations.”

### Design, Synthesis of Orally Bioavailable Novel Anaplastic Lymphoma Kinase (ALK) Inhibitor Diphenylaminopyrimidine Analogs and Efficacy Study on NCI-H2228 Xenografts Mice Model

“Within our ALK drug discovery program, we identified novel deuterated 2,4-diaryl amino pyrimidine compounds as potent ALK inhibitors. The compound 11 showed better IN VITRO activity and IN VIVO efficacy with good pharmacokinetic profile. IN VIVO efficacy of compound 11 was better than standard drug Ceritinib in NCI-H2228 xenograft mice model.”

### MiR-100-5p Confers Resistance to ALK Tyrosine Kinase Inhibitors Crizotinib and Lorlatinib in EML4-ALK Positive NSCLC

“In this study we sought to explore a possible involvement of microRNAs (miRNAs) in conferring resistance to ALK TKIs in ALK TKI-refractory NSCLC cell lines...The outcome of the combined approaches uncovered miR-100-5p to confer resistance to Crizotinib and Lorlatinib in EML4-ALK NSCLC cells and to be a potential therapeutic target in drug resistance.”

### Updated Efficacy and Safety Data and Impact of the EML4-ALK Fusion Variant on the Efficacy of Alectinib in Untreated ALK-positive Advanced Non-small-cell Lung Cancer in the Global Phase III ALEX Study

“Alectinib continues to demonstrate superior investigator-assessed PFS versus crizotinib in untreated ALK+ NSCLC, irrespective of EML4-ALK variant.”

### Relevance of Detection of Mechanisms of Resistance to ALK Inhibitors in ALK-Rearranged NSCLC in Routine Practice

“We identified 23 patients with advanced ALK-rearranged NSCLC who, between January 2012 and May 2017, had undergone at least one repeat biopsy at progression on an ALK TKI. A resistance mechanism was identified in 9 of the 23 patients (39%). The anomalies involved included 9 ALK mutations in 8 patients and one ALK amplification.”

### Renal Effects of Crizotinib in Patients With ALK-Positive Advanced NSCLC

“Crizotinib resulted in a decline in creatinine-based estimates of renal function mostly over the first 2 weeks of treatment. However, there was minimal evidence of effects with prolonged treatment and these changes were largely reversible following treatment discontinuation, consistent with previous reports suggesting this may be predominantly an effect on creatinine secretion as opposed to true nephrotoxicity.”

### Application of Time-dependent Modeling for the Exposure-efficacy Analysis of Ceritinib in Untreated ALK-rearranged Advanced NSCLC Patients

“Ceritinib 750 mg/day was approved for the treatment of patients with untreated anaplastic lymphoma kinase (ALK)-rearranged non-small cell lung cancer (NSCLC) based on ASCEND-4 study. The objective of this article is to introduce the use of time-dependent modeling approach in the updated exposure-efficacy analysis of Ceritinib for the first-line indication.”

### Ceritinib-related Interstitial Lung Disease Improving After Treatment Cessation Without Recurrence Under Either Crizotinib or Brigatinib: A Case Report

“Anaplastic lymphoma kinase inhibitors (ALKi) like Ceritinib are considered standard for front-line treatment of non-small cell lung cancers (NSCLC) harboring a translocation of the anaplastic lymphoma kinase (ALK) gene. We report herein a case of interstitial lung disease (ILD) that developed following a 7-month Ceritinib treatment without recurrence under either Crizotinib or Brigatinib, two others ALKi.”

### Optimal Management of Brain Metastases in Oncogenic-driven Non-small Cell Lung cancer (NSCLC)

“In this review, we discuss the current evidence on management of brain metastases and incorporate specific recent data on oncogenic-driven NSCLC in order to suggest recommendations on the optimal management of brain metastases in this subgroup of NSCLC where formal level I evidence is lacking.”

### Impact of EGFR Mutation and ALK Translocation on Recurrence Pattern After Definitive Chemoradiotherapy for Inoperable Stage III Non-squamous Non-small-cell Lung Cancer

“Although the ALK-positive group showed no characteristic failure pattern, the EGFR-mutant group showed a lower rate of in-field failure and higher rate of out-of-field failure.”

### Efficacy and Safety of Ceritinib (450 mg/d or 600 mg/d) With Food Versus 750-mg/d Fasted in Patients With ALK Receptor Tyrosine Kinase (ALK)-Positive NSCLC: Primary Efficacy Results From the ASCEND-8

“Ceritinib at a dose of 450 mg with food compared to 750-mg fasted showed consistent efficacy and less gastrointestinal toxicity.”

### Neoadjuvant Crizotinib in Resectable Locally Advanced Non-Small Cell Lung Cancer with ALK Rearrangement

“Neoadjuvant Crizotinib may be feasible and well tolerated in locally advanced disease for complete resection. Crizotinib therapy before surgery may provide thorough elimination of circulating molecular residual disease and not influence the reuse of first-line Crizotinib, but ongoing prospective trials are warranted to prove its efficacy in the neoadjuvant setting.”

### Discovery of 3,6-diaryl-1H-pyrazolo[3,4-b]pyridines as Potent Anaplastic Lymphoma Kinase (ALK) Inhibitors

“A new series of 3,6-diaryl-1H-pyrazolo[3,4-B]pyridine compounds have been discovered as potent anaplastic lymphoma kinase (ALK) inhibitors.”

### Next-generation Sequencing for ALK and ROS1 Rearrangement Detection in Patients With Non-small-cell Lung Cancer: Implications of FISH-positive Patterns

“Our data support that the identification of 3' isolated signal FISH pattern in ALK and ROS1 cases might suggest a false-positive result. NGS seems a reliable technique to assess ALK and ROS1 rearrangements, offering the advantage over immunohistochemistry of detecting other molecular alterations with potential therapeutic implications.”

### Diffuse Atypical Cystic Brain Metastases in ALK+ NSCLC Treated With Whole Brain Radiation and Second-Generation ALK-Targeted Therapy

“The patient received standard whole brain radiation therapy (WBRT) to a total radiation dose of 35 Gy, delivered over 14 treatments using 2.5 Gy per fraction. His treatment was switched from Crizotinib to Alectinib as well. Follow-up MRI after completion of radiation demonstrated a marked decrease in the size and number of cystic foci compared with those during prior examinations.”

### Prediction of ALK Mutations Mediating ALK-TKIs Resistance and Drug Re-Purposing to Overcome the Resistance

“Our results provide potential therapeutic strategies against some Lorlatinib- or Ceritinib-resistant compound mutations, and support the usefulness of our newly developed in silico computational simulation to predict resistance conferred by kinase mutations and effective candidate drugs.”

### Clinical Features and Therapeutic Options in Non-small Cell Lung Cancer Patients with Concomitant Mutations of EGFR, ALK, ROS1, KRAS or BRAF

“We compared the clinical features of 100 randomly selected patients harboring a single *ALK* rearrangement with those of the 20 patients harboring a coalteration with an *ALK* rearrangement but found no significant differences.”

### ALK Rearrangements: Biology, Detection and Opportunities of Therapy in Non-small Cell Lung Cancer

“Activating alterations of ALK confers an aggressive behavior and it is an important therapeutic target in NSCLC. Although there are several diagnostic methods to detect ALK rearrangements, FISH is the gold standard because its reliability and easy implementations in routine laboratories. On the other hand, despite the improvement of outcomes of ALK-positive NSCLC and although the current repertoire of ALK inhibitors include third-generation drugs, overcome the mechanisms of drug-resistance are greatest challenge.”

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