THE ALKFUSION REPORTER

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Welcome to ALKFUSION

Welcome to the February edition of *The ALKFusion Reporter.* In this edition, we see further research about various mechanisms of resistance that develop from ALK inhibitors. Interestingly, concomitant EGFR and ALK mutations can occur, underscoring how important it can be to obtain a biopsy upon progression.

Stay tuned for more developments coming out of the AACR Annual Meeting in late March!

Did we miss a study 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 Page or via the emails below.

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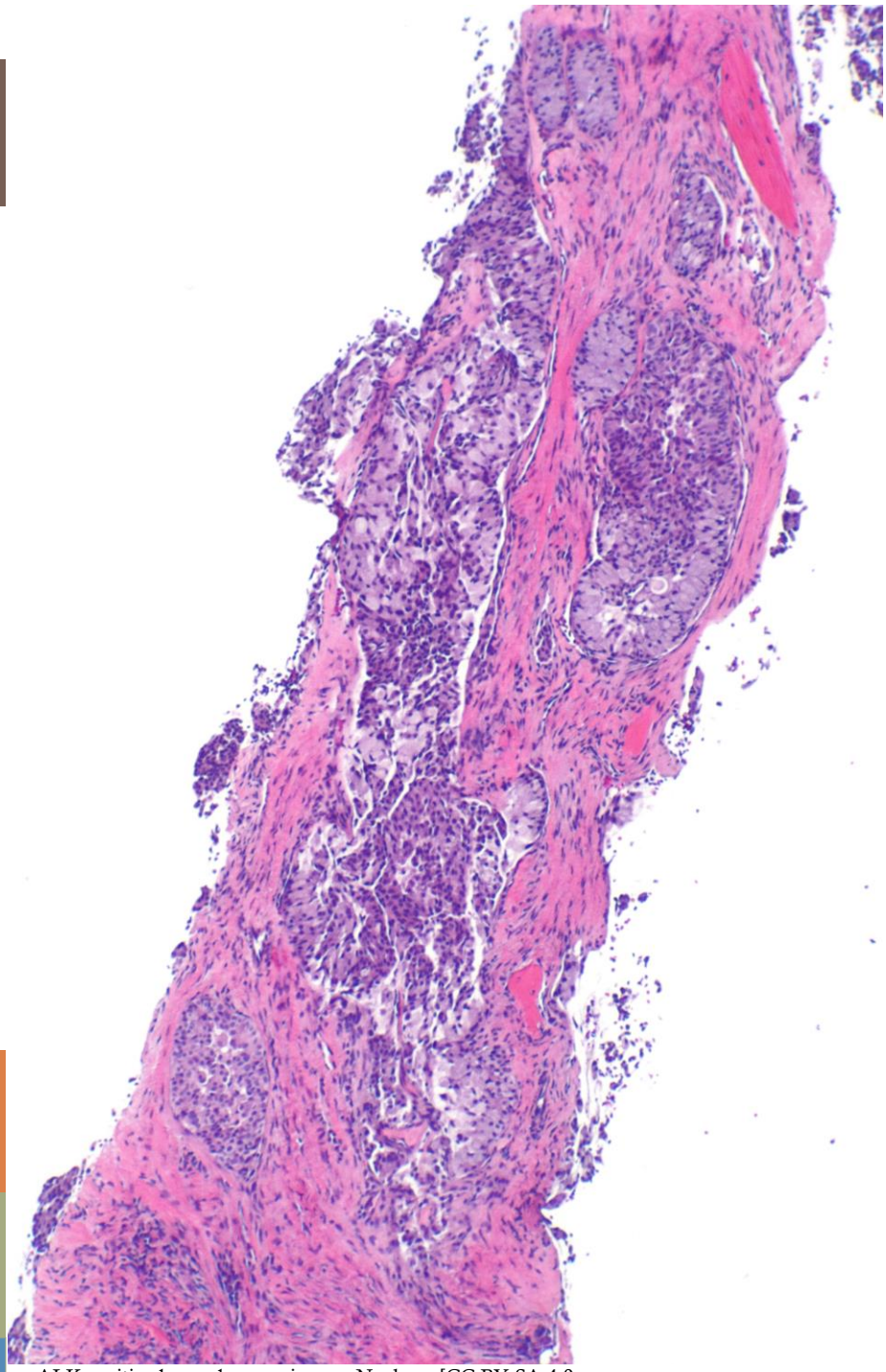

ALK positive lung adenocarcinoma, Nephron [CC BY-SA 4.0 (https://creativecommons.org/licenses/by-sa/4.0) or GFDL A(http://www.gnu.org/copyleft/fdl.html)], from Wikimedia Commons

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Oral Coadministration of Elacridar and Ritonavir Enhances Brain Accumulation and Oral Availability of the Novel ALK/ROS1 Inhibitor Lorlatinib

"Pharmacological inhibition of CYP3A4 reversed these effects, and simultaneous P-gp inhibition with elacridar boosted absolute brain levels of lorlatinib by 16-fold without obvious toxicity. These insights may help to optimize the clinical application of lorlatinib."

Crizotinib Enhances Anti-CD30-LDM Induced Antitumor Efficacy in NPM-ALK Positive Anaplastic Large Cell Lymphoma

"This research demonstrated for the first time that the combination of anti-CD30-LDM [CD30-targeting ADC] and crizotinib exhibits a synergistic inhibitory effect in tumor cells. These results provide scientific support for future clinical evaluations of anti-CD30-LDM, or other DNA-damaging agents, combined with NPM-ALK inhibitors."

Refining Precision Cancer Therapy in ALK-Positive NSCLC

"Collectively, these results highlight that structurally distinct, even earlier-generation, ALK-TKIs may be useful at different time points during the disease course as patients receive sequential ALK targeted therapies... In patients relapsing after multiple sequential therapies, tumours may harbour a greater degree of genomic complexity and heterogeneity that tempers the efficacy of any single ALK-TKI and effectively dampens the ALK-dependent phenotype… Thus, effective combinatorial approaches that address both ALK-dependent and ALK-independent resistance are needed. Together, these endeavours will help fine-tune our treatment approach to ALK-positive NSCLC to more precisely match the biology of the tumour."

Discordance Between FISH, IHC, and NGS Analysis of ALK Status in Advanced Non–Small Cell Lung Cancer (NSCLC): a Brief Report of 7 Cases

"These data highlight the role of IHC [Immunohistochemistry] and underscore the complexity of the genetic pattern of *ALK*. It could be crucial to consider these findings in order to best select patients for anti-ALK treatment in daily clinical practice."

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-1*H*-pyrazolo[3,4-*b*]pyridine compounds have been discovered as potent anaplastic lymphoma kinase (ALK) inhibitors."

Safety Issues with the ALK Inhibitors in the Treatment of NSCLC: A Systematic Review

"Most of adverse effects of ALKi can be managed efficiently via dose modifications or interruptions. Timely identification of each ALKi pattern of toxicity can prevent treatment-related morbidity and mortality in this palliative setting."

Clinical Utility of Cerebrospinal Fluid Cell-Free DNA as Liquid Biopsy for Leptomeningeal Metastases in ALK-Rearranged NSCLC

"Liquid biopsy of CSF [cerebrospinal fluid] is more sensitive than liquid biopsy of plasma to detect targetable alterations, characterizing resistance mechanisms on progression and monitoring tumor response in patients with *ALK*-rearranged NSCLC with LM [Leptomeningeal metastases.] Thus, CSF might be promising as a medium of liquid biopsy in LM."

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."

Activity of Brigatinib in the Setting of Alectinib Resistance Mediated by ALK I1171S in ALK-Rearranged Lung Cancer

"Here, we present what, to the best of our knowledge, is the first reported case in which alectinib resistance mediated by the *ALK*I1171S mutation was overcome by brigatinib."

Lung Cancer Family History and Exposure to Occupational/Domestic Coal Combustion Contribute to Variations in Clinicopathologic Features and Gene Fusion Patterns in Non-small Cell Lung Cancer

"ALK fusions and total gene rearrangement were closely associated with women, never smokers, younger age, FLC [family history of lung cancer], and coal exposure."

Concomitant Resistance Mechanisms to Multiple Tyrosine Kinase Inhibitors in ALK-Positive Non-small Cell Lung Cancer

"EML4-ALK variant 3 is the most frequent *ALK* variants in this cohort, followed by *EML4-ALK* variant 1. Half of the patients harbored *ALK* activating mutations upon progression on crizotinib treatment. After multi-TKIs treatment, 59% of the cases developed resistant *ALK* mutations, and concomitant *ALK* activating mutations were more commonly observed in this cohort ($P = 0.031$). Specifically, *ALK* G1269 A, L1196 M, and C1156Y substitutions were more common in crizotinib-alone samples, while *ALK*G1202R was significantly more enriched post-multi-TKIs ($P = 0.009$). Activated bypass signaling tended to be more prevalent in patients post-multi-TKIs. Furthermore, dual activation of ALK and bypass signaling was more frequently found in the multi-TKIs group (5/17, 29%) in contrast to crizotinib-alone (2/35, 6%) ($P = 0.031$). Additionally, concurrent *TP53* mutation demonstrated significantly shorter progression-free survival (PFS) compared with *TP53* wildtype in crizotinib-alone group (median PFS: 8 vs 13 months, Hazard Ratio = 1.494, $P = 0.019$)."

Safety and Effectiveness of Alectinib in a Real-World Surveillance Study in Patients with ALK-Positive NSCLC

"The 18-month cumulative OS rate was longer in patients with ECOG performance status ≤1 (versus 2 or ≥3; 83.7% versus 44.5% or 27.2%), without prior crizotinib (versus with; 81.1% versus 73.4%), receiving first-line alectinib (versus second and third or later line; 83.0% versus 79.2% or 71.9%), without brain metastases (versus with; 79.5% versus 71.5%). These data confirm the favorable safety and effectiveness of alectinib in patients with ALK-positive NSCLC in Japan."

Advance of Theragnosis Biomarkers in Lung Cancer: from Clinical to Molecular Pathology and Biology

"In this review, we summarize recent findings in *ALK*+-adenocarcinoma of the lung, highlighting the role of *TP53* mutations in this specific cancer type and suggest new diagnostic strategies for the future, in order to improve patient's outcome."

Concomitant Radiotherapy and TKI in Metastatic EGFR- or ALK-Mutated Non-small Cell Lung Cancer: a Multicentric Analysis on Behalf of AIRO Lung Cancer Study Group

"SRT seems to positively affect OS with limited toxicity in selected patients."

Anaplastic Lymphoma Kinase (ALK)-positive Tumors: Clinical, Radiographic and Molecular Profiles, and Uncommon Sites of Metastases in Patients With Lung Adenocarcinoma

"In NSCLC, ALK rearrangements may not be mutually exclusive mutations and can present with unique radiographic patterns. Patients with uncommon sites of metastasis may have worse outcomes."

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