THE ALKFUSION REPORTER

Issue No. 1 | DEC 2018/JAN 2019

Welcome to ALKFUSION

Welcome to the inaugural issue of *The ALKFusion Reporter*, the first summary of scientific research relating to ALK positive, non-small cell lung cancer written for ALK patients by ALK patients.

In this issue, you will see brief excerpts of ALK-related research published in December 2018 through early January 2019, together with links to the full article. Some articles, unfortunately, require a subscription for full access.

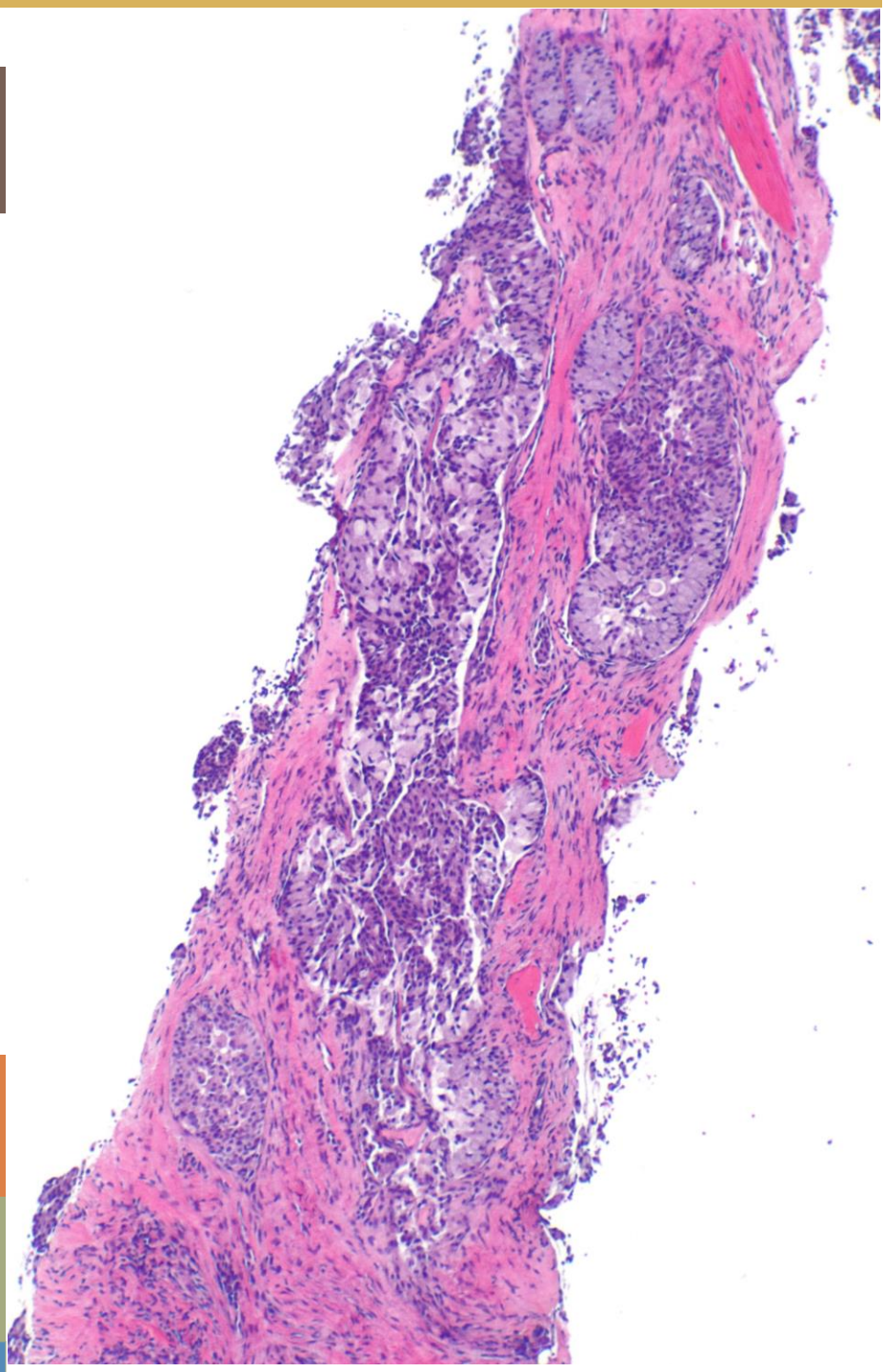
Our goal in providing this information to you is to help you become a more informed patient so that you can discuss these studies and findings with your oncologist. Put simply, an informed patient lives longer.

Did we miss a study in this issue you think should be included? Care to volunteer your talents to future issue of *The ALKFusion Reporter*? Contact us at the Facebook ALKFusion page!

INFORMED PATIENTS

LONGER LIVES

ALKFUSION



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

Continued on page 2

Ceritinib for an Anaplastic Lymphoma Kinase Rearrangement-Positive Patient Previously Treated with Alectinib with Poor Performance Status

"We report a patient with *ALK*-positive NSCLC who had previously been treated with first-line Alectinib. Rapid progression led to a poor PS [performance status]; however, Ceritinib here achieved a breakthrough in the clinical situation with a dramatic response, despite the poor PS."

Expression of Mucins (MUC1, MUC2, MUC5AC and MUC6) in ALK-positive Lung Cancer: Comparison with EGFR-mutated Lung Cancer

"The high frequency of both MUC1 and MUC5AC cytoplasmic expression, coupled with a lack of MUC2 and MUC6 expression in ALK+ lung cancer may contribute to the biologically aggressive behavior of ALK+ cancer. Inhibitors to these types of mucins may thus act as a barrier to cancerous extension reducing their aggressive behavior."

Adequacy of EBUS-TBNA Specimen For Mutation Analysis of Lung Cancer

"The aim of this study was to evaluate the adequacy of EBUS-TBNA [Convex probe endobronchial ultrasound (EBUS)-guided transbronchial needle aspiration (TBNA)] in providing adequate size specimens for *EGFR, ALK,* and *ROS1* genetic mutation analysis in patients with adenocarcinoma or Not Otherwise Specified (NOS) lung cancer...

The study demonstrated that EBUS-TBNA provides adequate material for mutation analysis in patients with newly diagnosed adenocarcinoma or NOS lung cancer."

ROS1 Gene Rearrangements are Associated with an Elevated Risk of Peri-Diagnosis Thromboembolic Events

"The risk of peri-diagnosis TEEs [thromboembolic events] is significantly elevated in patients with advanced ROS+ NSCLC compared to EGFR+ and KRAS+ cases. TEE risk may be similarly elevated in ALK+ NSCLC."

Clinical Outcomes of Patients with Resected, Early-stage ALK-positive Lung Cancer

"Among the 764 patients, 555 (73%), 101 (13%), and 108 (14%) had stage I, II, and III NSCLC, respectively. ALK-positive patients were distributed across all stages: 10 (34%) stage I, 6 (21%) stage II, and 13 (45%) stage III. Median [recurrence-free survival] RFS was not reached for EGFR-mutant patients, 24.3 months (95%CI 11.4–65.3) for ALK-positive patients, and 72.9 months (95%CI 59.7 to undefined) for KRAS-mutant patients. When adjusted for stage, ALK-positive NSCLC remained associated with worse RFS compared to EGFR-mutant (HR 1.8, 95%CI: 1.1-3.1), but not when compared to KRAS-mutant (HR 1.3, 95%CI: 0.8-2.1) NSCLC."

Lorlatinib Salvages CNS Relapse in an ALK-Positive Non–Small-Cell Lung Cancer Patient Previously Treated With Crizotinib and High-Dose Brigatinib

"We present a case of an ALK-positive patient who developed CNS metastases during treatment with Crizotinib, followed by a CNS response and then CNS disease progression during higher than licensed doses of Brigatinib, who was ultimately successfully treated with the third-generation ALK inhibitor Lorlatinib (PF-06463922)."

Clinical Relevance of PD-L1 Expression and CD8+ T Cells Infiltration in Patients with EGFR-mutated and ALK-rearranged Lung Cancer

"Patients with *EGFR* mutations or *ALK* rearrangements exhibited lower PD-L1 and CD8 co-expression level in TME [tumor microenvironment], which could be responsible for poor response to CPIs [check point inhibitors]. PD-L1 and CD8 co-expression in *EGFR*-mutated or *ALK*-rearranged lung cancer is a biomarker for poor prognosis with shorter OS."

Correlation Between Genetic Mutation State and Cancer-Associated Thrombosis in Advanced Cancer Patients

"There is no correlation between genetic mutation state and cancer-associated thrombosis in advanced cancer patients."

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

"ALK I1171X mutations seem to preferentially be Alectinib resistance mutations, and preclinical models of EML4-ALK plus ALK I1171N/S/T) proteins indicate that Ceritinib, Brigatinib, or Lorlatinib have putative sensitivity against them. To date, only Ceritinib had been reported by other groups to induce clinical responses in ALKI1171X–bearing Alectinib-resistant tumors. Our case report of clinical response to Brigatinib in ALK I1171S–positive lung cancer highlights the rapidly evolving management of advanced ALK-rearranged tumors and the role of clinically available liquid/tissue rebiopsies in guiding the sequencing of available or in-development ALK inhibitors."

Efficacy of Alectinib in Patients with ALK-Positive NSCLC and Symptomatic or Large CNS Metastases

"Of 19 patients, 15 (79%) had measurable CNS disease at baseline and were evaluable for response. CNS objective response rate (CORR) in these patients was 73.3% (95% CI, 44.9% to 92.2%), CNS disease control rate (CDCR) was 100.0% (95% CI, 78.2% to 100.0%), and median CNS duration of response (CDOR) was 19.3 months (95% CI, 14.3 months to not evaluable). ... All eight patients with symptoms attributable to CNS metastases had clinical improvement upon starting Alectinib. Six patients (32%) eventually required salvage brain radiotherapy."

Management of Brain Metastases in Non-small Cell Lung Cancer in the Era of Tyrosine Kinase Inhibitors

"The aim of this review is to summarize the current therapeutic landscape of brain metastases management in NSCLC, with a particular focus on EGFR-mutated and ALK-rearranged NSCLC subtypes."

Concurrent ALK/EGFR Alterations in Chinese Lung Cancers: Frequency, Clinical Features, and Differential Response to Therapy

"Among the 419 ALK rearranged lung cancers, a total of 21 patients (5.01%) were detected harboring concurrent ALK and EGFR (exon 18-20) genomic alterations. The concomitant rate of EGFR in patients harboring EML4-ALK (3.06%, 11/359) was dramatically lower than in non EML4-ALK patients (16.67%, 10/60, $p < 0.001$)."

Immunotherapy for Oncogenic-driven Advanced Non-small Cell Lung Cancers: Is the Time Ripe for a Change?

"[T]here are still several open questions about ICI [immune checkpoint inhibitors] in oncogenic-driven NSCLC, such as the efficacy and toxicities, which need to be addressed before considering treatment with ICI as a standard approach in this population. It is in this framework, we provide a thorough overview on this currently controversial topic."

Lung Adenocarcinoma with Concurrent ALK and ROS1 Rearrangement: A Case Report and Review of the Literatures

"Here, we report a 61-year-old male diagnosed with acinar adenocarcinoma, who was shown to have both ALK and ROS1 rearrangements but was EGFR- and C-MET mutation-negative."

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

"Concurrent ALK activating mutations and/or upregulated bypass signaling are more enriched in patients undergoing multiple ALK TKI treatments compared to Crizotinib alone. Concomitant TP53 mutation correlated to unfavorable survival when receiving a single TKI Crizotinib."

Natural history and factors associated with overall survival in stage IV ALK rearranged non-small-cell lung cancer

"110 ALK+ NSCLC patients were identified, 105 received crizotinib as their initial ALK inhibitor. With a median follow-up of 47 months, the median OS from diagnosis of stage IV disease was 81 months (6.8 years). Brain metastasis at diagnosis of stage IV disease (HR 1.01, p=0.971) and year of stage IV presentation (p=0.887) did not influence OS. More organs with tumor at diagnosis of stage IV disease associated with worse OS (HR 1.49 for each additional organ with disease including the CNS, p=0.002). Each additional month of pemetrexed based therapy associated with a 7% relative decrease in risk of death."

Efficacy and Safety of Lorlatinib in Korean Non-small-cell Lung Cancer Patients with ALK or ROS-1Rearrangement Who Failed Previous Tyrosine Kinase Inhibitor

"Patients with advanced NSCLC with ALK or ROS1 rearrangements who began lorlatinib between November 2016 and July 2018 were retrospectively analyzed. Twelve consecutive patients were included. The median age was 55 (range 36–76). Ten (83%) had ALK-positive NSCLC, and two (17%) had ROS1-positive NSCLC. All patients had a history of first- or second-generation ALK TKI use. Two ALK-positive patients and one ROS1-positive patient had the G1202R and G2032R mutations, respectively. The ORR was 64%, and the disease control rate (DCR) was 91%. Of the three ALK-positive patients with intracranial target lesions, one (33%) had a complete response, and two (67%) had a partial response, producing an intracranial objective response of 100%. The median PFS was 6.5 months (range 1.0–16.5)."

Histologic transformation of ALK-rearranged adenocarcinoma to squamous cell carcinoma after treatment with ALK inhibitor

"In this report, we described the first case of squamous cell carcinoma (SCC) transformation from adenocarcinoma (ADC) in NSCLC with ALK rearrangement after treatment with ALK TKI."

MYC Amplification as a Potential Mechanism of Primary Resistance to Crizotinib in ALK-Rearranged Non-Small Cell Lung Cancer: A Brief Report

"We postulate that the MYC gene may be implicated in the mechanism of primary resistance to ALK inhibitors. We also suggest potential MYC-directed inhibition strategies to overcome primary resistance in advanced ALK-rearranged NSCLC."

Rapid Progression of Metastatic Panspinal Epidural Non–Small Cell Lung Cancer After Discontinuation of Alectinib

"Recent termination of tyrosine kinase inhibitors or ALK inhibitors may result in severe disease flares, and a history of such should raise clinical suspicion for metastatic progression."

Pooled Safety Analysis for Two Generations ALK Inhibitors: A Meta Analysis

"[T]he ALK related serious adverse events [SAEs] should draw our attention especially the lung toxicity. According to this meta-analysis, Alectinib seems to be the safest ALK inhibitor."

TNM Staging Inversely Correlates with Age in ALK-positive Lung Cancer

"There was significant inverse correlation between age and clinical stages ($P < 0.001$). These laws also existed at various T, N, M categories. What was more, morbidity of ALK rearrangement manifested a steady downward trend with older age groups (≤40 vs. 40-49 vs. 50-59 vs. ≥60 years: 18.8% vs. 11.6% vs. 5.0% vs. 2.2%). Surprisingly, ALK-positive patients with stage IIIb-IV disease had much higher incidence than the patients with stage I-IIIa disease (6.1% vs. 3.4%, $P < 0.001$). Finally, the ALK-positive patients aged younger showed poorer outcomes compared with the older group."

Lorlatinib: a new-generation drug for ALK-positive NSCLC

"The results from this study establish Lorlatinib as a valuable addition for the treatment of ALK-rearranged tumours. The next step is to define the optimal place for Lorlatinib in the treatment sequence."

Lorlatinib in Patients with ALK-positive Non-small-cell Lung Cancer: Results from a Global Phase 2 Study

"Between Sept 15, 2015, and Oct 3, 2016, 276 patients were enrolled: 30 who were ALK positive and treatment naive (EXP1); 59 who were ALK positive and received previous Crizotinib without (n=27; EXP2) or with (n=32; EXP3A) previous chemotherapy; 28 who were ALK positive and received one previous non-Crizotinib ALK tyrosine kinase inhibitor, with or without chemotherapy (EXP3B); 112 who were ALK positive with two (n=66; EXP4) or three (n=46; EXP5) previous ALK tyrosine kinase inhibitors with or without chemotherapy; and 47 who were ROS1 positive with any previous treatment (EXP6). One patient in EXP4 died before receiving Lorlatinib and was excluded from the safety analysis set. In treatment-naive patients (EXP1), an objective response was achieved in 27 (90·0%; 95% CI 73·5–97·9) of 30 patients. Three patients in EXP1 had measurable baseline CNS lesions per independent central review, and objective intracranial responses were observed in two (66·7%; 95% CI 9·4–99·2). In ALK-positive patients with at least one previous ALK tyrosine kinase inhibitor (EXP2–5), objective responses were achieved in 93 (47·0%; 39·9–54·2) of 198 patients and objective intracranial response in those with measurable baseline CNS lesions in 51 (63·0%; 51·5–73·4) of 81 patients. Objective response was achieved in 41 (69·5%; 95% CI 56·1–80·8) of 59 patients who had only received previous Crizotinib (EXP2–3A), nine (32·1%; 15·9–52·4) of 28 patients with one previous non-Crizotinib ALK tyrosine kinase inhibitor (EXP3B), and 43 (38·7%; 29·6–48·5) of 111 patients with two or more previous ALK tyrosine kinase inhibitors (EXP4–5). Objective intracranial response was achieved in 20 (87·0%; 95% CI 66·4–97·2) of 23 patients with measurable baseline CNS lesions in EXP2–3A, five (55·6%; 21·2–86·3) of nine patients in EXP3B, and 26 (53·1%; 38·3–67·5) of 49 patients in EXP4–5.

The most common treatment-related adverse events across all patients were hypercholesterolaemia (224 [81%] of 275 patients overall and 43 [16%] grade 3–4) and hypertriglyceridaemia (166 [60%] overall and 43 [16%] grade 3–4). Serious treatment-related adverse events occurred in 19 (7%) of 275 patients and seven patients (3%) permanently discontinued treatment because of treatment-related adverse events. No treatment-related deaths were reported."

The Optimal ALK inhibitor in Advanced ALK-Positive NSCLC Patients: An Indirect Comparison Between Brigatinib and Alectinib

"Our study revealed that Brigatinib and Alectinib may be similar in terms of efficacy and safety for the first-line treatment of patients with ALK-positive NSCLC."

Variants Distribution and Heterogeneity of Outcomes to Crizotinib in ALK-Rearranged Chinese Non-Small Cell Lung Cancers

"This study demonstrated the distribution pattern of ALK rearrangements in Chinese NSCLCs, and illustrated the clinical outcomes of ALK-positive patients in different sub-groups."

Interstitial Lung Disease Onset and its Risk Factors in Japanese Patients with ALK-positive NSCLC Following Treatment with Crizotinib

"Crizotinib therapy should be applied to the NSCLC patients with any of above risk factors under a cautious monitoring for ILD occurrence, and clinicians should pay attention to the risks of severe ILD."

Afatinib Reverses Ceritinib Resistance (CR) in ALK/ROS1-positive Non-small-cell Lung Cancer Cell (NSCLC) via Suppression of NRG1 Pathway

"[A]fatinib overcame CR in NSCLC cells with positive ALK or ROS1 by inhibiting the NRG1 signaling pathway, which might be a promising therapeutic approach."

Identification of a High-Level MET Amplification in CTCs and cfTNA of an ALK-Positive NSCLC Patient Developing Evasive Resistance to Crizotinib

"This study shows the clinically relevant gain of a MET amplification in CTCs and cfTNA after treatment with Crizotinib inducing primary resistance to ceritinib and Alectinib. Our data further underline the potential of liquid biopsies to reflect tumor heterogeneity and inform clinical decision making."

Clinical Outcome of Crizotinib in Diverse ALK Fusion Partners and Different Detection Methods Treatment Naïve Advanced NSCLC

"In subgroups analysis of different ALK fusion patterns, patients with exclusive ALK fusion pattern were shown to have a longer PFS than those carrying dual ALK fusion patterns. (12m vs. 6.5m, p = 0.02). Comparing with non-EML4 fusion partners, EML4 fusion partners have the longer PFS (12.0m vs. 6.8m, p=0.04)."

Safety issues with the ALK inhibitors in the treatment of NSCLC: A systematic review

"To adequately describe the exact safety profile of each of those agents we conducted a systematic review of prospective trials testing various ALK inhibitors (ALKi) in NSCLC. We compare common AE with each ALKi along with clinical approach to management."

Clinical Value of Local Therapy in Advanced Crizotinib-Treated ALK-Rearranged Lung Cancer: Pattern of Failure Analyses

"Among patients with BBM, brain radiotherapy before Crizotinib provide considerable clinical benefits. Conversely, deferring extra-cranial local therapies until after initial Crizotinib-treatment failure and adopting regular surveillance may be a better treatment strategy for metastatic lesions outside the brain."

The Effect of a High-Fat Meal on the Pharmacokinetics of Brigatinib, an Oral Anaplastic Lymphoma Kinase Inhibitor, in Healthy Volunteers

"Consumption of a high-fat meal decreased the rate of Brigatinib oral absorption but had no impact on the extent of absorption, thereby supporting Brigatinib administration without regard to meals. These recommendations are reflected in the US prescribing information for Brigatinib."

Dramatic Response to Alectinib in a Lung Cancer Patient with a Novel VKORC1L1-ALK Fusion and an Acquired ALK T1151K Mutation

"Here, we report a novel VKORC1L1-ALK fusion and an ALK T1151K resistance mutation detected in a lung cancer patient who had been on Crizotinib for over 8 years. Alectinib induced a dramatic response in this patient demonstrating its clinical activity against T1151K."

THE ALKFUSION REPORTER

INFORMED PATIENTS

LONGER LIVES

ALKFUSION