THE ALKFUSION REPORTER

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The ALKFusion Reporter

Here are the latest results from studies of ALK positive lung cancer. Each title includes a link to the abstract or full text article.

Have any suggestions or comments? Want to help with an edition of the *Reporter,* please contact the editors,

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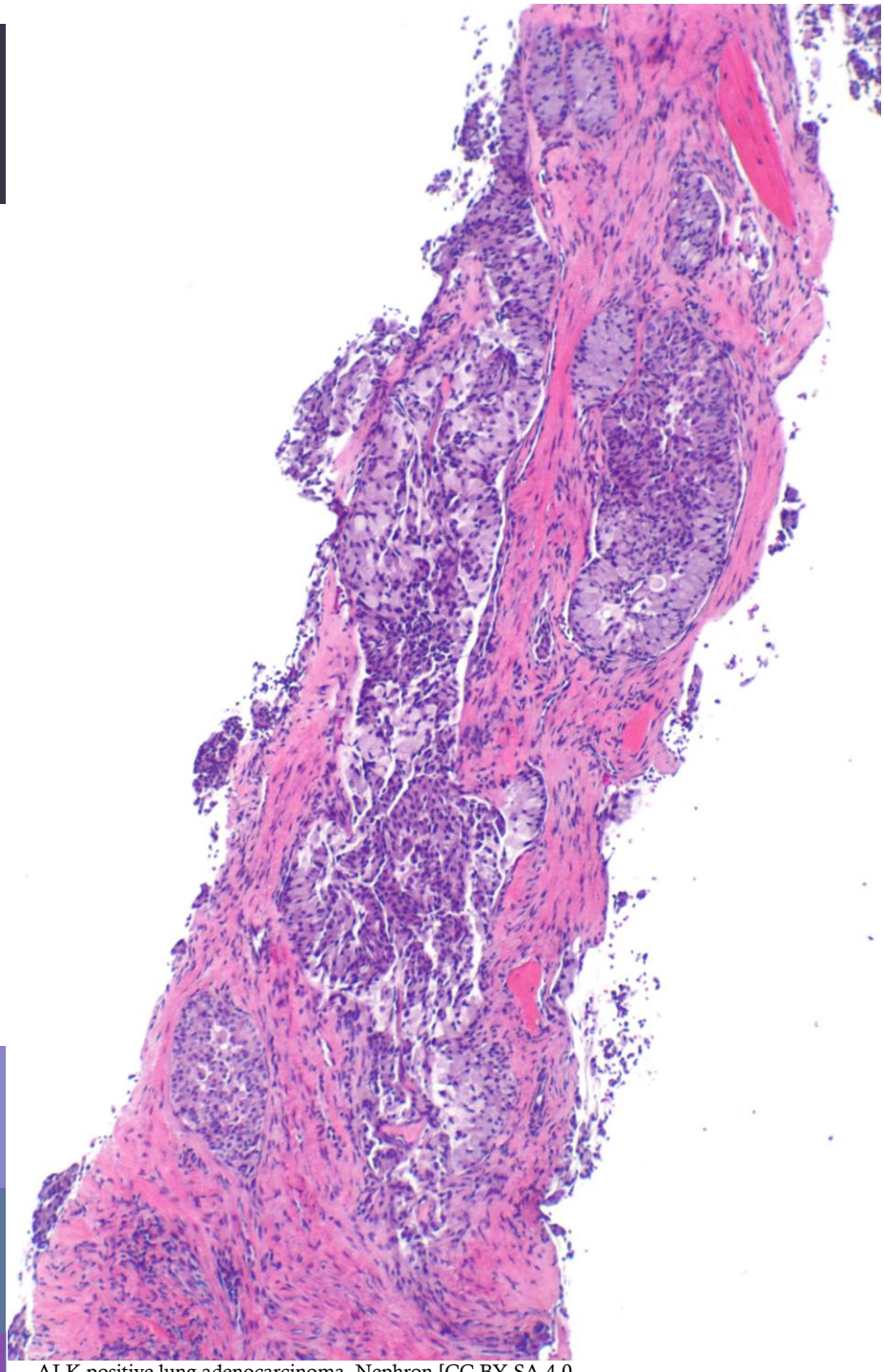

ALK positive lung adenocarcinoma, Nephron [CC BY-SA 4.0 (https://creativecommons.org/licenses/by-sa/4.0) or GFDL A(http://www.gnu.org/copyleft/fdl.html)], from Wikimedia Commons

INFORMED PATIENTS

LONGER LIVES

ALKFUSION

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Acquired Resistance Mutations to ALK-Inhibitors Identified by Single Circulating Tumor Cell Sequencing in ALK-Rearranged Non-Small-Cell Lung Cancer

"Our results highlight the genetic heterogeneity and clinical utility of circulating tumor cells to identify therapeutic resistance mutations in *ALK*-rearranged patients...Single-CTC sequencing may be a unique tool to assess heterogeneous resistance mechanisms and help clinicians for treatment personalization and resistance options to ALK-targeted therapies."

Treatment Optimization for Brain Metastasis from Anaplastic Lymphoma Kinase Rearrangement Non-Small-Cell Lung Cancer

"Brain metastasis is common in non-small-cell lung cancer (NSCLC) with driver gene mutations... However, there are relatively few studies specified on the treatment of brain metastasis from *ALK*gene rearrangement NSCLC... This review focuses on new data on the prognosis of *ALK*-TKI and the proper combination model of *ALK*-TKI with radiotherapy... ***Key Messages:*** Next-generation *ALK*-TKIs are now replacing crizotinib as first-line treatment in *ALK*i-naïve *ALK*rearrangement NSCLC patients with brain metastasis, and they alone might have a strong efficacy against intracranial tumors in crizotinib-refractory situations in which occasion radiotherapy might be omitted. SRS and WBRT are both local treatment options for brain metastasis."

Prospective Detection of Mutations in Cerebralspinal Fliud, Pleural Effusion, and Ascites of Advanced Cancer Patients to Guide treatment Decisions

“Many advanced cases of cancer show central nervous system (CNS), pleural or peritoneal involvement. In this study, we prospectively analyzed if cerebrospinal fluid (CSF), pleural effusion (PE) and/or ascites can be used to detect driver mutations and guide treatment decisions... The results of testing of CSF, PE and ascites were used to guide treatment decisions, such as initiation of osimertinib treatment or selection of specific ALK tyrosine - kinase inhibitors. In conclusion, fluids close to metastatic sites are superior to blood for the detection of relevant mutations and can offer valuable clinical information, particularly in patients progressing to targeted therapies.”

An Exploration of Solvent-Front Region High Affinity Moiety Leading to Novel Potent ALK & ROS1 Dual Inhibitors with Mutant-combating Effects

Ceritnib Analogs 8-42 were identified as ALK & ROS1 inhibitors. #39 displayed remarkable antitumor effects on ALK & ROS1-addicted cancer cells... #39 displayed impressive mutant-combating effects in cellular and enzymatic assays. #39 induced apoptosis of H2229 cell line in a dose-dependent manner... Finally, the binding models of #**39** with ALK^{wt}, ROS1, ALK^{L1196M} and ALK^{G1202R} were ideally established which further clearly elucidated their mode of action within the active site.

Multiplex Flourescense in Situ Hybridisation to Detect Anaplastic Lymphoma Kinase and ROS Proto-Oncogene 1 Receptor Tyrosine Kinase Rearrangement in Lung Cancer Cytological Samples

"In most lung cancer patients, the biological materials available to morphological and molecular diagnosis are exclusively cytological samples and minimum tumour wastage is necessary. Multiplex fluorescence in situ hybridisation (mFISH) to detect simultaneously ALK-rearrangement and ROS-1 rearrangement on a single slide could be useful in clinical practice to save cytological samples for further molecular analysis.... CONCLUSION:Multiplex ALK/ROS1 FISH probe test is a useful tool to detect simultaneously *ALK*-rearrangement and *ROS1*-rearrangement on a single slide in cytological specimens with a small amount of biomaterial.

Discovery of 2-aminopyridines Bearing a Pyridone Moiety as Potent ALK Inhibitors to Overcome the Crizotinib-Resistant Mutants

"2-Aminopyridine derivatives with 2-pyridone ring were designed and synthesized. **18d** was identified with a significant inhibition against ALK-addicted cancer cells. **18d** demonstrated superior potency against ALK^{WT}, ALK^{L1196M}, ALK^{G1202R} and ROS1. **18d** induced G1-phase cell cycle arrest in Karpas-299 (81.5%)... Taken together, this work provided a promising ALK inhibitor to circumvent the clinical crizotinib-resistant mutants.

Two Cases of Krukenberg Tumors from ALK-Rearranged Lung Adenocarcinoma: An Uncommon Site of Metastasis

"To the Editor:...Krukenberg tumors account for 1% to 2% of ovarian tumors. In all, 70% originate from the stomach, with most of the remainder originating from other gastrointestinal malignancies.[4] We found few other reported cases of Krukenberg tumors from NSCLC, yet all but one harbored an ALK mutation, potentially indicating that ALK-positive NSCLC tumors have preferential tropism to the ovaries.[5] ... Surgical resection is the typical strategy for management of Krukenberg tumors. However, both of our patients had a durable response to ALK inhibitors. Therefore, in these cases a trial of ALK-targeted therapy should be considered initially, as it could lead to prolonged disease control."

Rapid Postoperative Relapse in ALK-Positive Locally Advanced NSCLC Patient with Complete Pathological Response to Neoadjuvant Crizotinib

To the Editor:... The patient is a 34-year-old male patient in whom lung adenocarcinoma and metastatic mediastinal lymph nodes were diagnosed and who received neoadjuvant crizotinib for 2 months... Complete surgical resection was successfully performed. ..The patient received adjuvant crizotinib for 3.6 months and discontinued treatment because of a personal issue. .. Meanwhile, positron emission computed tomography was performed. We found multiple enlarged lymph nodes and a suspected hilar lesion with a significantly increased standardized uptake value.. After 3 months' treatment with crizotinib, a computed tomography scan showed major tumor regression (–80%); the patient continues taking crizotinib.

The Clinical Responses of TNIP2-ALK Fusion Variants to Crizotinib in ALK-Rearranged Lung Adenocarcinoma

"...*ALK* rearrangements have been previously identified in about 5.1% of lung adenocarcinoma, including *EML4-ALK* fusion variants, *KIF5B-ALK* and *TFG-ALK*. However, a *TNIP2-ALK* fusion has not been reported in lung adenocarcinoma. Herein, we described a rare case of *ALK*-rearranged lung adenocarcinoma responding to crizotinib."

ALK Immunohistochemistry Positive, FISH Negative NSCLC is Infrequent, but Associated With Impaired Survival Following Treatment with Crizotinib

"ALK IHC + FISH- NSCLC is infrequent and associated with a worse outcome on personalized treatment. A suitable predictive testing strategy may be to screen first with IHC and then confirm with FISH instead of considering ALK IHC equivalent to ALK FISH according to the current guidelines."

Complete Pathological Response to Crizotinib in a Patient with ALK-rearranged Lung Adenocarcinoma

"The identification of anaplastic lymphoma kinase (ALK) gene fusions as actionable oncogenic drivers in lung cancers led to the development and approval of multiple ALK tyrosine kinase inhibitors (TKIs); the first of these was crizotinib. .. Here, we report the first complete pathological response to first-line crizotinib in a patient with ALK-rearranged lung cancer."

Pooled Overall Survival and Safety Data From the Pivotal Phase II Studies (NP28673 And NP28761) of Alectinib in ALK-Positive Non-Small-Cell Lung Cancer

"Updated results from this pooled analysis further demonstrate that alectinib has robust clinical activity and a manageable safety profile in patients with advanced, *ALK*+ NSCLC pretreated with crizotinib."

Efficacy, Safety, and Biomarker Analysis of Ensartinib in Crizotinib-Resistant, ALK-Positive Non-Small-Cell Lung Cancer: A Multicentre, Phase 2 Trial

"We aimed to assess the efficacy and safety of ensartinib in ALK-positive patients with non-small-cell lung cancer (NSCLC), in whom crizotinib therapy was unsuccessful. 52% ...had an objective response... 70%... with measurable brain metastases... had an intracranial objective response... 91%... had at least one treatment-related adverse event, which were mostly grade 1 or 2... Ensartinib has activity and is well tolerated in patients with crizotinib-refractory, ALK-positive NSCLC, including those with brain metastases."

Clinical Observation of Crizotinib in the Treatment of ALK-Positive Advanced Non-Small Cell Lung Cancer

"The clinical and pathological data of 87 patients confirmed to have NSCLC by pathology or cytology were selected from April 2014 to January 2017 at the Tumor Hospital of Hebei Province...The objective response rate (ORR) was 61.7%, the disease control rate (DCR) was 93.6%, and the mPFS was 19 months... The efficacy of crizotinib in patients with advanced NSCLC is related to the number of metastatic organs, age and timing of treatment. The use of crizotinib is prone to intracranial progression, and progression of simple brain metastases is not an indication that crizotinib is discontinued. Patients will continue to benefit from combination of local radiotherapy."

Ceritinib Plus Nivolumab in Patients With Advanced ALK-Rearranged Non-Small-Cell Lung Cancer: Results of an Open-Label, Multicenter, Phase 1B Study

Ceritinib plus nivolumab has activity; ORR appears to correlate with PDL1 at baseline. Toxicity, especially rash, is more common than with either single agent.

Cytotoxicity of Curcumin Derivatives in ALK Positive Non-Small Cell Lung Cancer

"Non-small cell lung cancer with ALK rearrangements can be targeted effectively with ALK inhibitors such as crizotinib. However, cancer progression typically occurs within a year as drug resistance develops... The cytotoxicity of curcumin, RL66, and RL118 were tested in both ALK^+ lung cancer cells (H3122), crizotinib resistant ALK^+ cells (CR-H3122) and ALK^- lung cancer cells (A549), both alone and in combination with crizotinib... ALK^+ cells were 2-3x more sensitive to RL66 and RL118 than ALK^- cells, with the drugs' eliciting IC_{50} values in the range of 0.7–1 μM in H3122 cells."

Efficacy of Platinum/Pemetrexed Combination Chemotherapy in ALK-Positive Non-Small Cell Lung Cancer Refractory to Second-Generation ALK Inhibitors

"Platinum/pemetrexed-based chemotherapy shows modest efficacy in *ALK*-positive NSCLC after failure of second-generation ALK TKIs. The activity may be higher if administered with an ALK TKI, suggesting a potential role for continued ALK inhibition."

A Compound L1196M/G1202R ALK Mutation in a Patient with ALK-Positive Lung Cancer With Acquired Resistance to Brigatinib Also Confers Primary Resistance to Lorlatinib

In conclusion, we show here for the first time that a drug-resistant compound $ALK^{L1196M/G1202R}$ mutation can arise against brigatinib in patients with NSCLC. Unfortunately, the double mutation identified here also conferred resistance to lorlatinib, further limiting treatment options for the patient,"

Rapid Acquisition of Alectinib Resistance in ALK-Positive Lung Cancer With High Tumor Mutation Burden

"High tumor mutation burden and heterogeneous tumor evolution might be responsible for rapid acquisition of alectinib resistance. Timely lorlatinib administration or combined therapy with an ALK inhibitor and other receptor tyrosine-kinase inhibitors might constitute a potent strategy."

Monitoring Therapeutic Response and Resistance: Analysis of Circulating Tumor DNA in Patients With ALK+ Lung Cancer

"Clinical utility of ctDNA was shown, both at pre-treatment by identifying a potential subgroup of ALK+ NSCLC patients who may derive more benefit from ensartinib and longitudinally by tracking resistance. Prospective application of this technology may translate to improved outcomes for NSCLC patients treated with ALK TKIs."

Early Onset Pulmonary Toxicity With Lorlatinib in a Patient With Previous Pulmonary Toxicity From Brigatinib

"Our case describes a patient with ALK-rearranged NSCLC who developed pulmonary toxicity on brigatinib that recurred after exposure to lorlatinib at early onset."

Novel Derivatives of Anaplastic Lymphoma Kinase Inhibitors: Synthesis, Radiolabeling, and Preliminary Biological Studies of Fluoroethyl Analogues of Crizotinib, Alectinib, and Ceritinib

"Highlights: Anaplastic lymphoma kinase (ALK) is a therapeutic target in lung cancer. Many ALK inhibitors are routinely used for therapy of lung cancer. The blood-brain barrier remains a challenge for treatment of brain metastasis. [19F/18F]Fluoroethyl analogues of ALK inhibitors have been developed and tested. Preliminary in vitro and in vivo PET imaging pharmacokinetic results were encouraging, showing significant brain penetration."

Patient-Reported Outcomes from the Randomized Phase III ALEX Study of Alectinib Versus Crizotinib in Patients With ALK-Positive Non-Small-Cell Lung Cancer

"We present patient-reported outcomes (PROs) from ALEX to assess disease burden, treatment-related symptom tolerability, and health-related quality of life (HRQoL) with alectinib versus crizotinib... Conclusion: PRO data support the superior efficacy and tolerability of alectinib relative to crizotinib demonstrated in the ALEX study."

ROS-Dependent DNA Damage Contributes to Crizotinib-Induced Hepatotoxicity Via The Apoptotic Pathway

"Highlights: Crizotinib causes hepatocellular damage via the apoptotic pathway. Mitochondrial membrane potential (MMP) decrease is involved in crizotinib-induced apoptosis. Crizotinib induces reactive oxygen species (ROS) generation and DNA damage. Crizotinib-induced hepatotoxicity is independent of ALK, ROS1 and MET."

A Novel ALK Inhibitor ZYY Inhibits Karpas299 Cell Growth in Vitro And in a Mouse Xenograft Model and Induces Protective Autophagy

"Highlights: ZYY is a novel synthetic ALK inhibitor derived from ceritinib.ZYY inhibits Karpas299 cell growth *in vitro* and *in vivo* without evident toxicity.ZYY induces apoptosis and autophagy in Karpas299 cells.Autophagy inhibition enhances ZYY-induced Karpas299 cell apoptosis and cytotoxicity."