

THE ALKFUSION REPORTER

Issue No. 6 | August/September 2019

The ALKFusion Reporter with Special World Lung Preview

As summer winds to close, researchers have remained busy. In addition to the usual articles, we have a preview of the upcoming IASLC World Lung Cancer Conference in Barcelona this September. Advances from World Lung include several interesting clinical trials that are still enrolling, and reports on effective usage of MET inhibitors in ALK patients. Stay tuned for live updates from some of our ALKFusion members!

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

Laura Greco (99lmgreco@gmail.com)

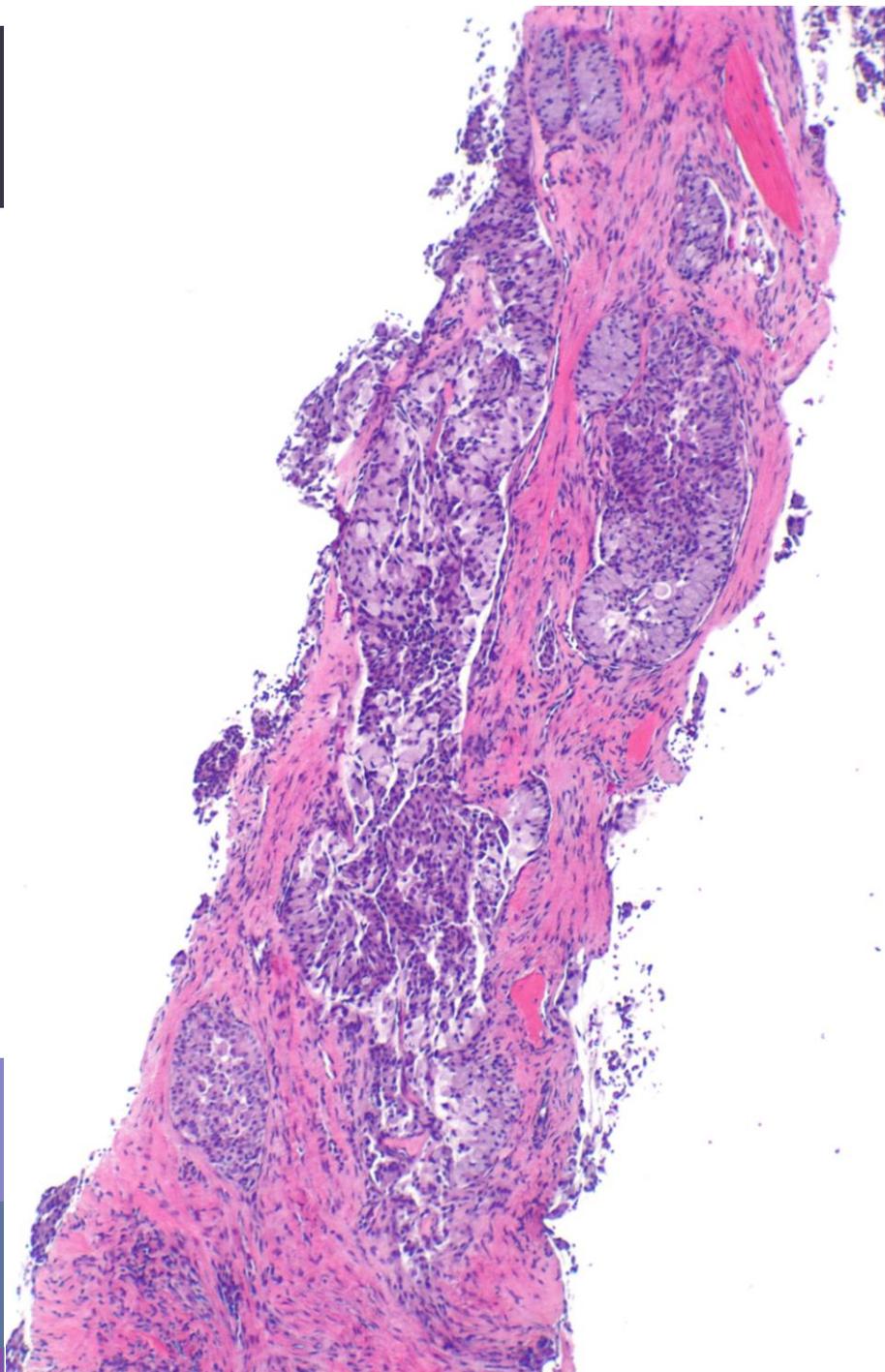
or

Jennifer Cosgrove
(jencos@gmail.com).

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

“Although several ALK inhibitors, including crizotinib, ceritinib, and alectinib, are approved for cancer treatment, their long-term benefit is often limited by the cancer's acquisition of resistance owing to secondary point mutations in ALK. Importantly, some ALK inhibitors cannot cross the blood-brain barrier (BBB) and thus have little or no efficacy against brain metastases. The introduction of a lipophilic moiety, such as a fluoroethyl group may improve the drug's BBB penetration. Herein, we report the synthesis of fluoroethyl analogues of crizotinib, alectinib, and ceritinib, and their radiolabeling with ^{18}F for pharmacokinetic studies.”

[Curcumin as Tyrosine Kinase Inhibitor in Cancer Treatment](#)

“The targets in oncological therapy are, among others, tyrosine kinases, important mediators of signaling pathways whose impaired expression is observed in many types of cancer.... Current research is aimed at modifying structures that improve the pharmacokinetic parameters of curcumin, e.g. the formation of nanoparticles, complexes with metals or the synthesis of curcumin derivatives with functional substituents that allow tumor targeting. The article is a review and analysis of current literature on the properties of curcumin and its derivatives in the treatment of cancers directed to signaling pathways of tyrosine kinases and confronts the problem of low assimilation of curcumin with potential therapeutic effects.”

[Systemic Therapy for Brain Metastases](#)

“Although cancer treatment is improving overall, central nervous system metastases are becoming more prevalent and require finesse to properly treat. Physicians must consider the biology of the primary tumor and the complex neurological environment that the metastasis resides in.... Therefore, this review seeks to update the reader on recent advancements made on the three most common sources of brain metastases: lung cancer, breast cancer, and melanoma.”

[Design, Synthesis and Biological Evaluations of 2-amino-4-\(1-Piperidine\) Pyridine Derivatives as Novel Anti Crizotinib-Resistant ALK/ROS1 Dual Inhibitors](#)

“Aiming to explore new potent inhibitors, a series of 2-amino-4-(1-piperidine) pyridine derivatives that stabilized a novel DFG-shifted conformation in the kinase domain of ALK were designed and synthesized on the base of lead compound A. Biological evaluation highlighted that most of these new compounds could also potently inhibit ROS1 kinase, leading to the promising inhibitors against both ROS1 and ALK....molecular modeling disclosed that all the representative inhibitors could dock into the active site of ALK and ROS1, which gave a probable explanation of anti Crizotinib-resistant mutants. These results indicated that our work has established a path forward for the generation of anti Crizotinib-resistant ALK/ROS1 dual inhibitors.”

[The Clinical Impact of Family History of Cancer in Female Never-smoker Lung Adenocarcinoma](#)

“Accumulating evidence reveals the association between the risk of never-smoker lung cancer and family history of cancer....ALK/ROS1/RET fusions are enriched in patients with family history of nonlung cancer.”

[Synthesis and Anti-tumor Efficacy of Novel 2, 4-Diarylamino-pyrimidine Derivatives Bearing N-\(3-Pyridinylmethyl\) Urea Moiety as Anaplastic Lymphoma Kinase Inhibitors](#)

“Compound 5m suppressed phosphorylation of ALK and its downstream proteins, and showed low cytotoxicity on normal human primary fibroblast cells (BJ cells)... Interestingly, compound 5m also showed broader anti-proliferative activity on other human tumor cell lines, which was different from other ALK inhibitors.”

[Next-generation Sequencing Identified a Novel WDPCP-ALK Fusion Sensitive to Crizotinib in Lung Adenocarcinoma](#)

“An increasing number of ALK alteration rearrangements, including point mutations and genomic amplification, have been detected using NGS-based techniques, and preclinical and early clinical trials are constantly exploring potential targets and new treatment options. Individualized and precise treatment based on molecular biology will be the target and direction of future treatments.... In recent years, other fusion types sensitive to crizotinib, such as DYSF&ITGAV-ALK, BCL11A-ALK, and BIRC6-ALK, have been discovered by next-generation sequencing (NGS). However, a WD (Trp-Asp) planar cell polarity (PCP) effector gene (WDPCP)-ALK fusion has not been previously published....we report this novel WDPCP-ALK fusion, which is sensitive to crizotinib, in a patient with lung adenocarcinoma.”

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

“Clinical utility of ctDNA was demonstrated, both at pre-treatment by identifying a potential subgroup of ALK+ NSCLC patients that 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.”

Brigatinib in Patients with ALK-Positive Advanced Non-small-cell Lung Cancer Pretreated With Sequential ALK Inhibitors: A Multicentric Real-world Study (BRIGALK Study)

“These real-world results confirm the efficacy of brigatinib in a cohort of patients heavily pretreated for ALK-positive advanced NSCLC.”

Transformation to Neuroendocrine Carcinoma as a Resistance Mechanism to Lorlatinib

“Small cell transformation is a well-recognized mechanism of resistance to EGFR-TKI therapy in EGFR-mutant NSCLC, yet it remains a poorly-described phenomenon in ALK-rearranged NSCLC....Given the inevitable development of resistance in ALK + NSCLC, if feasible, re-biopsy on progression should be standard over liquid biopsy. Neuroendocrine carcinoma transformation remains an important mechanism of acquired resistance to lorlatinib.”

IASLC World Lung Preview

There are MANY abstracts and posters at this year's World Lung Conference dealing with ALK. Below is a link to the webpage (from which you can search for ALK Abstracts). For your reference, below are summaries of the abstracts. We look forward to reporting on the presentations and posters themselves!

https://library.iaslc.org/conference-program?product_id=15&author=&category=&date=&session_type=&session=&presentation=&keyword=&available=&cme=&page=5

OA02.07 - Phase 3 ALUR Study of Alectinib in Pretreated ALK+ NSCLC: Final Efficacy, Safety and Targeted Genomic Sequencing Analyses

“The ALUR (NCT02604342) primary analysis (cut-off January 2017) demonstrated improved efficacy and safety with alectinib versus chemotherapy in patients with ALK+ NSCLC previously treated with chemotherapy and crizotinib. These patients can develop crizotinib resistance through ALK secondary mutations, but limited data exist regarding alectinib's efficacy in patients with different post-crizotinib genetic profiles. We report final data from ALUR including treatment outcomes according to genetic profile.”

OA02.06 - The Sequential Therapy of Crizotinib Followed by Alectinib: Real World Data of 840 Patients with NSCLC Harboring ALK-Rearrangement (WJOG9516L)

“Previous clinical trials demonstrated that alectinib (ALEC) had a longer time-to-progression than crizotinib (CRZ) in 1st-line settings. Information on long-term overall survival (OS), however, is still limited with a few studies having reported that the sequential strategy of “CRZ followed by other ALK-inhibitor” can provide extended OS. In Japan, ALEC was approved for a 1st-line setting earlier than in other countries.... The combined TTF in the CRZ group was significantly longer than TTF in the ALEC group, however, OS benefit of sequential therapy of CRZ followed by ALEC was not shown.”

EP1.01-26 - Non-Small Cellular Pulmon Cancer ALK Positive in Pediatrics

“This case report is from a 14-year-old adolescent patient treated in our institution with an ALK inhibitor. We report the experience of a case with excellent tolerability to an inhibitor of ALK, and its clinical benefit, (partial response and stable disease). Patients under 18 years, are excluded in most clinical trials and can benefit from treatment, increase in progression-free survival, overall survival, avoiding the toxicity of chemotherapy.”

EP1.01-35 - Concurrent Use of Low Dose Aspirin and Vitamin D in ALK, ROS and EGFR Mutant NSCLC: A Single Institution Retrospective Analysis

“Our study did not show any differences in PFS or DCR [disease control rate] in EGFR, ROS and ALK positive NSCLC patients who were concurrently taking vitamin D or aspirin compared with those who were not. Our study was small and was not powered to pick up any significant differences. Given the strong pre-clinical background, further prospective studies would be interesting to evaluate the synergistic benefit of vitamin D and aspirin with concurrent TKI use.”

EP1.01-56 - Co-Presentation of Adenocarcinoma and Squamous Cell Lung Carcinoma Harboring ALK Rearrangement in Different Sites

“We describe an unique case of co-presentation of ADC and SCC in two different disease sites, both harbouring ALK rearrangement.”

EP1.01-62 - The Safety Profile and Preliminary Efficacy of Ceritinib 450mg with Food in Chinese ALK/ROS-1 Positive NSCLC Patients

“This first-time real-world study aims to assess the safety profile and preliminary efficacy of Ceritinib 450mg with food in Chinese patients....Ceritinib 450mg with food demonstrated a good safety profile and efficacy with lower AE incidence rate and better compliance rate compare to ASCEND-8 data for Chinese patients in real-world setting.”

EP1.03-32 - Prevalence of EGFR and ALK Mutations in Non Small Cell Lung Cancer in Viet Nam National Cancer Hospital

“The prospective study of formalin fixed paraffin embedded (FFPE) tissues from patients diagnosed with NSCLC was performed to assess the prevalence of EGFR and ALK mutations in NSCLC in Viet Nam National Cancer Hospital...In this study investigating the prevalence of EGFR and ALK mutations in non small cell lung cancer in Vietnam National Cancer Hospital, 26.2% had EGFR mutation and 10.7% had ALK translocation mutations.”

EP1.08-07 - Correlation Between Genetic Profiling and Response in Danish ALK-Positive NSCLC Patients Treated with Crizotinib

“Although this small cohort does not allow [us] to draw unambiguous conclusions, it does indicate that the efficacy of treatment may vary with different *ALK*-fusion-partners. Moreover, *ALK*-positive NSCLC should be validated and classified by NGS-testing at baseline to optimize the choice of ALK-TKI.”

EP1.09-17 - Spanish Lung Cancer Biomarker Testing Registry (Lungpath): Descriptive Analysis Focus in ALK Translocation Results

“*LungPath* is an on-line tool developed by the Spanish Society of Pathology (*SEAP*) with free and voluntary participation of different[] Departments of Pathology to registry, monitor and trace biomarker results in clinical practice. After initial data reclutation [sic] step, first objective is to realize a descriptive analysis of *LungPath* focusing on ALK traslocation [sic] testing.”

EP1.14-02 - Comparative Efficacy of First-Line Ceritinib at a Dose of 450mg with Food and Alectinib in Advanced ALK+ NSCLC

“Although a previous cross-study indirect study compared the efficacy of ceritinib 750-mg fasted with alectinib, the efficacy of ceritinib 450-mg fed compared with alectinib is unknown... In the cross-study indirect comparison, the efficacy of ceritinib 450-mg fed was comparable with alectinib with numerically lower hazard of progression or death. However, results from indirect comparison can be limited by unobserved or unmeasured confounding. Head-to-head randomized phase III trials are needed to formally compare the efficacy of ceritinib 450-mg fed vs Alectinib with the literature reports.”

EP1.14-03 - Driver Genes as Predictive Indicators of Brain Metastasis in Patients with Advanced NSCLC: EGFR and ALK as Well as RET Gene Mutations

“Brain metastasis is a cause of disease progression and death in lung cancer patients, and is also one of the most common metastatic sites of lung cancer. Non-small lung cancer (NSCLC) accounts for about 80% of all lung cancer patients, and adenocarcinoma has become the main subtype of NSCLC in recent years. A retrospective analysis verified the role of gene mutations in brain metastasis in patients with non-small lung cancer (NSCLC). ... Of the 552 patients with advanced NSCLC, 153 (27.7%) had brain metastases. Univariate analysis showed that age ($P = 0.008$), gender ($P = 0.016$), smoking history ($P = 0.010$), lymph node metastasis ($P = 0.003$), and three driver genes: positive EGFR mutation ($P = 0.001$), positive ALK gene fusion ($P = 0.021$) and positive RET gene fusion ($P = 0.003$) were factors influencing the incidence of brain metastasis. Logistic multivariate regression analysis revealed that only positive EGFR mutation ($P = 0.012$), positive ALK gene fusion ($P = 0.015$), positive RET gene fusion ($P = 0.003$), pathological type ($P = 0.009$), lymph node N2–3 metastasis ($P = 0.000$) and a younger age ($P = 0.000$) were independent risk factors for brain metastasis. In addition, a ROC curve was plotted with the above factors with $AUC=0.705$ ($P=0.000$)...EGFR mutation, ALK gene fusion and RET gene fusion in advanced NSCLC patients play roles in brain metastasis as positive driver genes.”

EP1.14-07 - Efficacy and Safety of ALK Inhibitors in ALK-Rearranged Non-Small Cell Lung Cancer: A Systematic Review and Meta-Analysis

“This meta-analysis is the first, to our knowledge, to report an OS improvement with the use of ALK [inhibitors] vs. chemo. A trend toward a better OS was also seen with ALK 2G vs. ALK 1G and this is likely because of crossover effects and limited OS follow-up. Longer follow up and further research are warranted to directly compare ALK inhibitor sequences and to understand the outcomes of 2nd generation ALK inhibitors as initial therapy.”

▪ EP1.14-51 - Lorlatinib in Crizotinib-Resistant ALK+ NSCLC Patients. Our Experience

“Lorlatinib, [] the third generation inhibitor of ALK and ROS1 tyrosine kinase, has shown activity in patients with crizotinib-refractory ALK-positive NSCLC most of whom had CNS metastases. We report results of the overall and intracranial antitumor activity of patients with crizotinib- [sic] refractory ALK-positive NSCLC. Our results confirmed that lorlatinib is an effective treatment option for pretreated ALK+/ROS1+ patients with high intracranial activity and good safety profile.

EP1.14-47 - Lung Adenocarcinoma with Concurrent KRAS Mutation and ALK Rearrangement Responding to Crizotinib

“We reported a rare case of 47-year-old female was diagnosed with lung adenocarcinoma and treated with three cycles of chemotherapy. A biopsy acquired after disease progression revealed concurrent *KRAS* mutation and *ALK* translocation by a NGS assay.”

EP1.14-52 - Variants Distribution and Clinical Outcomes to Crizotinib According to Molecular Features in ALK-Rearranged NSCLCs

“This study explored the correlation of molecular characteristics and clinical outcomes to crizotinib in *ALK*-positive patients. This study illustrated the distribution pattern of *ALK* fusions in Chinese NSCLCs, and demonstrated the differential clinical outcomes of *ALK*-rearranged patients according to specific molecular features. This study might improve basic knowledge of the heterogeneous responses of *ALK*-positive patients to crizotinib and provide guidance for clinicians to design appropriate treatment on *ALK*-positive NSCLCs.”

EP1.16-28 - ALK Translocated Patients: Survival in an Unselected Population

“Median OS was 32 months (IQR 15-78). 1-year, 2-year and 3- year survival was 75%, 69% 49.9% respectively....The ALK translocation and targeted treatments have led to a dramatic improvement in overall survival in clinical trials confirmed in our series.”

EP1.16-32 - Percentage of ALK Rearrangement as a Response Predictor in Non-Small Cell Lung Cancer Treatment

“Our study aimed to correlate the percentage of ALK rearrangement found as a predictor of response in NSCLC ALK-positive treatment... We found that there is no statistical correlation between the percentage of ALK rearrangement and the PFS, OS, or the response rate in our patients, whatever the line of therapy. Nevertheless, there is an improvement in RR, PFS and consequently in OS among patients with ALK inhibitors in first line.”

P1.01-24 - Preclinical Proteomic Evaluation of Alternating ALK TKI Therapy Versus Continuous Dosing in ALK NSCLC to Inform the ALKternate Clinical Trial

“ALKternate is a clinical trial recruiting pre-treated patients, testing the hypothesis that with fixed alternating TKI therapy, the emergence of ALK resistant clones can be suppressed through applying variable selection pressure compared to continuous treatment with a TKI. This has been tested pre-clinically with a human cell line to complement the clinical trial in progress.”

P1.01-93 - Metastases Sites as a Prognostic Factor in a Real-World Multicenter Cohort Study of Spanish ALK-Positive NSCLC Patients (p)

“We aim to evaluate the effect of number of metastases (M1) organs on overall survival (OS) in a multicenter cohort of Spanish ALK-positive NSCLC p diagnosed between 2008 and 2017. ...OS was worse with increased metastatic sites involved at diagnosis in p with ALK positive NSCLC, being liver M1 associated with the highest risk of mortality. Brain metastases at diagnosis were not a prognostic factor for OS in our series.”

P1.01-129 - Preclinical Genetic Evaluation of Alternating ALK TKI Therapy Versus Continuous Dosing in ALK NSCLC to Inform the ALKternate Clinical Trial

This contains the preclinical justification for the ALKternate clinical trial that is currently recruiting.

P1.03-15 - Non-Invasive Detection of Secondary Resistance Mutations in ALK-Positive NSCLC Patients by Next-Generation Sequencing

“Secondary ALK-TKI resistance mutations could be detected using liquid biopsies in a high proportion of patients. Non-invasive molecular profiling of samples collected at disease progression is feasible being useful for further treatment selection in ALK-positive NSCLC patients.”

P1.14-01 - Are Pretreatment Inflammation-Based Prognostic Scores Useful in Predicting the Outcomes of Patients with ALK-Positive NSCLC?

“An increased systemic inflammatory response has been shown to be associated with a poor prognosis, and some of the parameters used to characterize this response can easily be measured in clinical practice in several tumor types but have not been analyzed extensively in ALK+ lung cancer in the era of crizotinib...In a cohort of patients with ALK positive NSCLC treated with crizotinib in routine practice, elevated pre-treatment SII was associated with shorter OS and PFS in univariate analysis and PNI was associated with shorter OS in multivariate analyses. Moreover, the mGPS and PNI were associated with lower response rates.”

P1.14-07 - Genomic Profiling of Liquid Biopsies During 2nd/3rd Generation ALK Inhibitor Therapy to Identify Novel Mechanisms of Resistance

“Somatic alterations from plasma cfDNA were detected in all six patients at various time points with three patients having detectable ALK alterations. Systemic progression (2/2 patients) correlated well with the ability of liquid biopsies to detect somatic mutations, while central nervous system (CNS)-predominant progression did not (4/4 patients). One patient, after disease progression on ceritinib, alectinib and brigatinib, exhibited variable allele fractions (AFs) of ALK G1202R mutation in cfDNA. The levels of G1202R decreased and ultimately became undetectable, corresponding to the patient’s clinical response to lorlatinib. In a patient who exhibited significant systemic progression, a massive increase in mutation AFs and many newly acquired mutations were detected in the cfDNA, including NOTCH1, DICER1, BRCA2, TP53, CDKN2A, ERBB3, and FAT1 mutations. However, the increase in the number of co-mutations was not related to increases in the amount of extracted cfDNA.”

P1.14-09 - Unveiling Hidden MET-Mediated Primary Alectinib Resistance in ALK-Positive Non-Small Cell Lung Cancer

“Alectinib is an ALK inhibitor that is currently used for the treatment of ALK-positive NSCLC. This next generation ALK inhibitor was initially used as second-line therapy following resistance to crizotinib. More recently, alectinib has superseded crizotinib, an ALK/ROS1/MET inhibitor, as a first-line therapy due to its superiority in phase III trials. Although patients enjoy durable responses to alectinib, they eventually develop resistance. Here we describe four cases of primary resistance to alectinib in which the patients show little to no response to alectinib when administered as first or second-line therapy....We show that MET is a critical component and serves as a bypass mechanism of alectinib resistance either alone or in combination with AXL or ERBB3. We also demonstrate that crizotinib could overcome MET-mediated ALK resistance in a patient.”

P1.14-15 - Lorlatinib in ALK- or ROS1-Positive Non-Small Cell Lung Cancer Patients: Experience from an Early Access Program in Turkey

“In this EAP, lorlatinib showed systemic activity in patients with advanced ALK+ or ROS1+ NSCLC, regardless of CNS metastases and previous TKI treatment.”

P1.14-18 - ALK Inhibitor Sequencing and Outcomes Among ALK-Positive (ALK+) NSCLC Patients in the US Community Oncology Setting

“This study provides an initial view of treatment patterns following the emergence of new ALK inhibitors and suggests feasibility of sequential ALK therapies. Follow-up studies will help improve understanding of outcomes of patients treated with 2nd generation-led sequences.”

P1.14-26 - ALK Fusion Variant Detection by Targeted RNA-Seq in TKIs Treated ALK-Positive Lung Adenocarcinoma

“[A] significant difference in the mean duration of the different ALKi treatment was found according to the ALK variants (Chi-square $p < 0.0001$), suggesting a private ALKi efficacy profile for specific fusion variants. Finally, the 3 HIP-ALK cases showed a better outcome with respect the EML4-ALK variants (not reached vs 51 months). Our analysis suggests that different ALK fusion variant might affect ALKi treatment duration in ALK+ lung ADC.”

P1.14-32 - Rash and Efficacy in Anaplastic Lymphoma Kinase Positive (ALK+) Non-Small Cell Lung Cancer Patients Treated with Ensartinib

“Ensartinib is a potent ALK small molecule tyrosine kinase inhibitor (TKI). In a phase 1/2 study, ensartinib was generally well tolerated and demonstrated good clinical activity in pts with ALK+ non-small cell lung cancer (NSCLC). This post hoc analysis sought to determine the relationship between ensartinib-related rash and clinical benefit...Ensartinib was associated with mild to moderate rash that was easily managed. Preliminary findings suggest that rash is potentially associated with better clinical benefit with ensartinib.”

P1.14-35 - Epithelial-To-Mesenchymal Transition Is a Mechanism of ALK Inhibitor Resistance in Lung Cancer Independent of ALK Mutation Status

ALK rearrangement, most commonly EML4-ALK, is detected in approximately 3%–5% of NSCLC. ALK tyrosine kinase inhibitor (TKI), shows dramatic clinical efficacy, however, almost all patients acquire resistance over time. The most defined mechanism of crizotinib resistance is secondary ALK mutations. A recent study reported that epithelial-to-mesenchymal transition (EMT) and ALK resistance mutation were simultaneously detected in a single tumor lesion in patients with ALK-rearranged lung cancer who were resistant to ALK-TKIs. However, it is still unknown whether ALK-TKI

resistant tumor cells combine mesenchymal phenotype with ALK resistance mutation, or each of the mesenchymal type tumor cells and ALK resistance mutation–positive cells coexist in a single lesion.... These findings indicate that HDAC inhibitor pretreatment followed by a new ALK inhibitor may be useful to circumvent resistance constituted by coexistence of resistance mutations and EMT in the heterogeneous tumor.”

P1.14-39 - Acquired ALK Rearrangement in EGFR-Mutant Lung Adenocarcinoma Treated with EGFR TKIs

“The frequency of acquired *ALK* rearrangement is similar in *EGFR*-mutant lung adenocarcinomas after resistance to the first-, second-, or third-generation EGFR TKIs. The majority of acquired *ALK*-fusion partners are non-*EML4*. Combination of EGFR TKIs and ALK inhibitors might be a strategy to overcome such resistance.”

P1.14-43 - A Novel Patient Derived Synchronous Cell Pair with Different Mutations in an ALK-Rearranged Lung Adenocarcinoma Underlines Tumor Heterogeneity

“We established a novel synchronous ALK-translocated lung ADC cell pair from the malignant pleural effusion (PF240-PE) and the pleural carcinosis (PF240-PC) of a 38-year-old female patient following sequential ALK targeted therapy.... We identified two distinct resistance mutations in both tissue specimens: a so far non-characterized E1161K and the already described L1152R. Strikingly, PF240-PC harbored E1161K and PF240-PE carried L1152R.”

P1.14-53 - Co-Occurring CDKN2A/2B Alteration Is Associated with Poorer Survival in ALK-Positive Lung Cancer

“We analyzed whether variants or co-occurring mutations influence the outcome of ALK TKI treatment in ALK+ non-small-cell lung cancer (NSCLC). The similar median PFS was observed in patients ALK variant 3 and non-variant 3 regardless of first ALK TKI treatment strategy (crizotinib, 18.9 vs. 15.2 months, $p=0.35$; alectinib, both not reached). As a co-occurring mutation, TP53 mutation was detected in 17 (45.9%) patients. And there was no statistical difference in PFS or OS between the wild type and TP53 mutation group [PFS 18.2 vs 15.3 months, $p=0.92$; OS 62.1 vs 62.2 months, $p=0.44$]. CDKN2A/2B alteration was the second most common mutation and observed in 9 (24.3%) patients. Median PFS and OS in ALK-CDKN2A/2B co-mutated patients were lower than wild type patients [PFS 15.3 months (95% CI: 8.1-22.5) versus 18.2 months (95% CI: 13.0–23.4), $P=0.064$, OS 26.7 months (95% CI: 14.2–39.3) versus not reached, $P=0.022$].”

P1.14-57 - Post-Ensartinib Outcomes in Refractory Anaplastic Lymphoma Kinase (ALK)-Rearranged Non-Small Cell Lung Cancer (NSCLC)

“Ensartinib is well tolerated and has clinical activity in advanced ALK-rearranged NSCLC patients with brain metastases, despite previously progressing on crizotinib, with durable post-ensartinib survival on subsequent next-generation ALK inhibitors such as brigatinib and lorlatinib.”

P1.16-28 - The Humanistic Burden of ALK+ NSCLC: Findings from the ALKConnect Patient Insight Network and Research Platform

“ALKConnect gathered humanistic burden data directly from patients with ALK+ NSCLC. Participants reported that the most burdensome symptoms were fatigue, sleep disturbance, and drowsiness, and that symptoms interfered most with work and general activity. A 3-month delay in cancer progression and HRQoL were important treatment attributes. Patients’ HRQoL was positively associated with ALK TKI treatment and the ability to maintain employment status, suggesting that these aspects may be important for ALK+ NSCLC patients’ well-being.”

P1.16-30 - Impact of Patient TKI Copayments on Insurance Expenditure in Advanced EGFR or ALK Positive Non-Small Cell Lung Cancer (NSCLC)

“We evaluated the effect of patient TKI copayments on insurance expenditures among patients with EGFR and ALK positive advanced NSCLC receiving TKIs. Eliminating TKI copayments would reduce patient financial burden and not adversely impact insurer spending.”

P1.16-46 - Genetic Testing Patterns, Treatment Characteristics, and Overall Survival in ALK-Positive Metastatic NSCLC Patients Treated with Ceritinib

“This study ...sought to assess ALK testing patterns, treatment characteristics, and overall survival (OS) in patients with mNSCLC treated with ceritinib in routine practice...Median OS following the first-line therapy initiation was nearly 3 years among the selected study patients.”

P1.18-04 - Neoadjuvant Ceritinib for Locally Advanced Non-Small Cell Lung Cancer with ALK Rearrangement: SAKULA Trial

“Our results showed that neoadjuvant ceritinib is safe and effective, with a high rate of pathologic response, in patients with ALK-positive resectable LA-NSCLC, although the limitation of the data interpretation due to small sample size.”

PC01.03 - Real World Research Groups - ALK+ Group

“There is a natural tension inherent to clinical trials—between scientific rigor and a participant’s hope that an experimental therapy shall prove effective. However, it is important to never lose track of the reason for clinical trials. ...Clinical trials cannot happen without the cooperation of human participants. That

cooperation is referred to as compliance. A patient who is noncompliant risks ejection from a trial. This creates a relationship that is inherently unbalanced. It is possible to address both accrual and the needs of the participant if clinical trials become truly patient centric. To do so one must consider the burden of participation. A clinical trial should be viewed as an opportunity, albeit one that is not risk free. Lessening the burden and removing some of the barriers to participation will better address the needs of both patients and the field of medical research.”

P2.01-04 - NCI-NRG Oncology ALK PROTOCOL (NRG-LU003): A Biomarker-Driven Protocol for Previously Treated ALK-Positive Non-Squamous NSCLC Patients

NRG-LU003 proposes to study ALK-positive non-squamous NSCLC patients who develop resistance to a second-generation ALK inhibitor, in order to establish a treatment algorithm for these patients based on resistance mechanisms. Patients will undergo tissue biopsy along with blood sampling for cfDNA analysis. One of the aims of the study is to establish the concordance between tissue and liquid biopsies; liquid biopsy may replace tissue biopsy after the first 200 patients enrolled, depending on the concordance and in consultation with CDRH/FDA. Treatments will be selected based on preclinical and clinical data demonstrating activity of treatment particular inhibitor against the specific ALK mutation or resistance mechanism identified. If no ALK resistance mutations are identified, patients will be randomized to receive either a next-generation ALK inhibitor they have not previously received or pemetrexed-based therapy with cisplatin or carboplatin.”

P2.01-11 - ALKternate: A Proof of Concept Study in ALK-Rearranged NSCLC Alternating Lorlatinib with Crizotinib After Disease Progression

ALKternate is a proof of concept open label multi-centre translational study alternating lorlatinib (100mg OD) with crizotinib (250mg BD) (Figure 1. including eligibility). The aim is to identify whether this fixed alternating schedule of ALK TKI is: safe; feasible and active, resulting in prolonged systemic and intracranial disease control via delaying the emergence of ALK TKI resistance. A secondary aim is to investigate whether plasma ALK-dependent and independent resistance profiles can be used to monitor therapy effectiveness.

P2.01-31 - Preliminary Results of Second Generation ALK Inhibitor PLB1003: A Phase Ia Study

“ALK rearrangements have been described in approximately 4-5% of patients with non-squamous non-small cell lung cancer (NSCLC). Crizotinib is initially effective in the treatment of ALK-rearranged NSCLC, but the disease eventually progresses. PLB1003, a high-efficiency second generation ALK inhibitor, was developed due to the increased resistance of EML4-ALK fusion genes. Preclinical data show that PLB1003 is safe and effective in cell-based assays and Crizotinib-resistant animal models. This is the ongoing phase Ia study of PLB1003.”

P2.01-35 - Acquired MET-Aberrance Is a Mechanism of Resistance to ALK Inhibitors in ALK-Positive Advanced Non-Small-Cell Lung Cancer

“Unfortunately ALK-positive NSCLC patients treated with ALK TKIs inevitably develop resistance mediated by complex mechanisms including ALK mutations, ALK amplification, or activation of alternative signaling pathways...MET-aberrance was defined as c-Met overexpression performed by immunohistochemical(IHC) staining method with SP44 antibody and MET amplification assessed by tumor tissue or plasma Next-generation sequencing (NGS) or fluorescent in situ hybridization(FISH)...Totally 5.89% (8/136) of patients were identified with MET-aberrance in 136 ALK-rearranged cases. Among the 8 patients, there were 6 with DE NOVO MET-aberrance and 2 with acquired MET-aberrance. The median progression-free survival (PFS) in ALK-rearranged patients with DE NOVO MET-aberrance was 9.6 months (95% CI 0.0 to 19.2months).The other 2 patients gained MET-aberrance after the treatment with lorlatinib. Both of them received lorlatinib, but the PFS only lasted for 2months. One achieved partial remission with crizotinib, which was originally developed as an inhibitor of the MET gene.”

MA18.07 – Identification of Neuroendocrine Transformation in Anaplastic Lymphoma Kinase Rearranged (ALK+) Tumors After Tyrosine Kinase Inhibitors

“Acquired resistance after ALK tyrosine kinase inhibitors treatment has multiple known mechanisms: new mutations or gene amplifications, bypass signaling and rarely neuroendocrine histological transformation. Here we describe results of a program utilizing routine biopsy post-progression in ALK+ patients for clinical and research purposes...Routine combined clinical and research biopsy of ALK+ patients at time of TKI failure helped to identify these recent cases of neuroendocrine transformation as a possible mode of resistance and provide tissue for model development. This is the first time that ALK+ transformation to large cell neuroendocrine carcinoma is reported in the literature.”

MA21.05 - Phase II Trial of the Combination of Alectinib with Bevacizumab in ALK-Positive Nonsquamous Non-Small Cell Lung Cancer

“Alectinib is a 2nd generation highly selective anaplastic lymphoma kinase (ALK) inhibitor. Although alectinib has improved progression-free survival (PFS) in patients with ALK-positive Non-Small Cell Lung Cancer (NSCLC), there are limited treatment options after progression of alectinib. Recent evidences have described promising results of the combination of bevacizumab with EGFR-TKIs, cytotoxic chemotherapies and immune-checkpoint inhibitors. We report the results from a phase II study of the combination of alectinib with bevacizumab in ALK-positive Nonsquamous NSCLC patients who were treated with alectinib and showed disease progression... Patients with ALK+ Nonsquamous NSCLC who had progressed after alectinib treatment were enrolled. Primary objective of this study was PFS and safety. Secondary endpoints included overall survival, objective response rate and disease control rate...The objective response rate and disease control rate were 8% and 67%, respectively... This is the first study to investigate the combination of alectinib and bevacizumab. This combination had clinical efficacy and was well tolerated.”