THE ALKFUSION REPORTER

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Welcome to The Reporter ASCO Special Edition

It's almost June, so it's ASCO time! In this edition, we highlight the most recent ALK research, as always. In addition, we provide, beginning on page 3, ALK-related research that will be presented at ASCO's annual meeting in Chicago May 31-June 5.

Further information and comments about some of the ASCO abstracts, posters, and presentations can be found on Twitter at @ALK_fusion and on Facebook Page at ALKFusion. Spread the word!

Have any suggestions or comments? Please contact the editors, Laura Greco (99lmgreco@gmail.com) or Jennifer Cosgrove (jencos@gmail.com).

INFORMED PATIENTS

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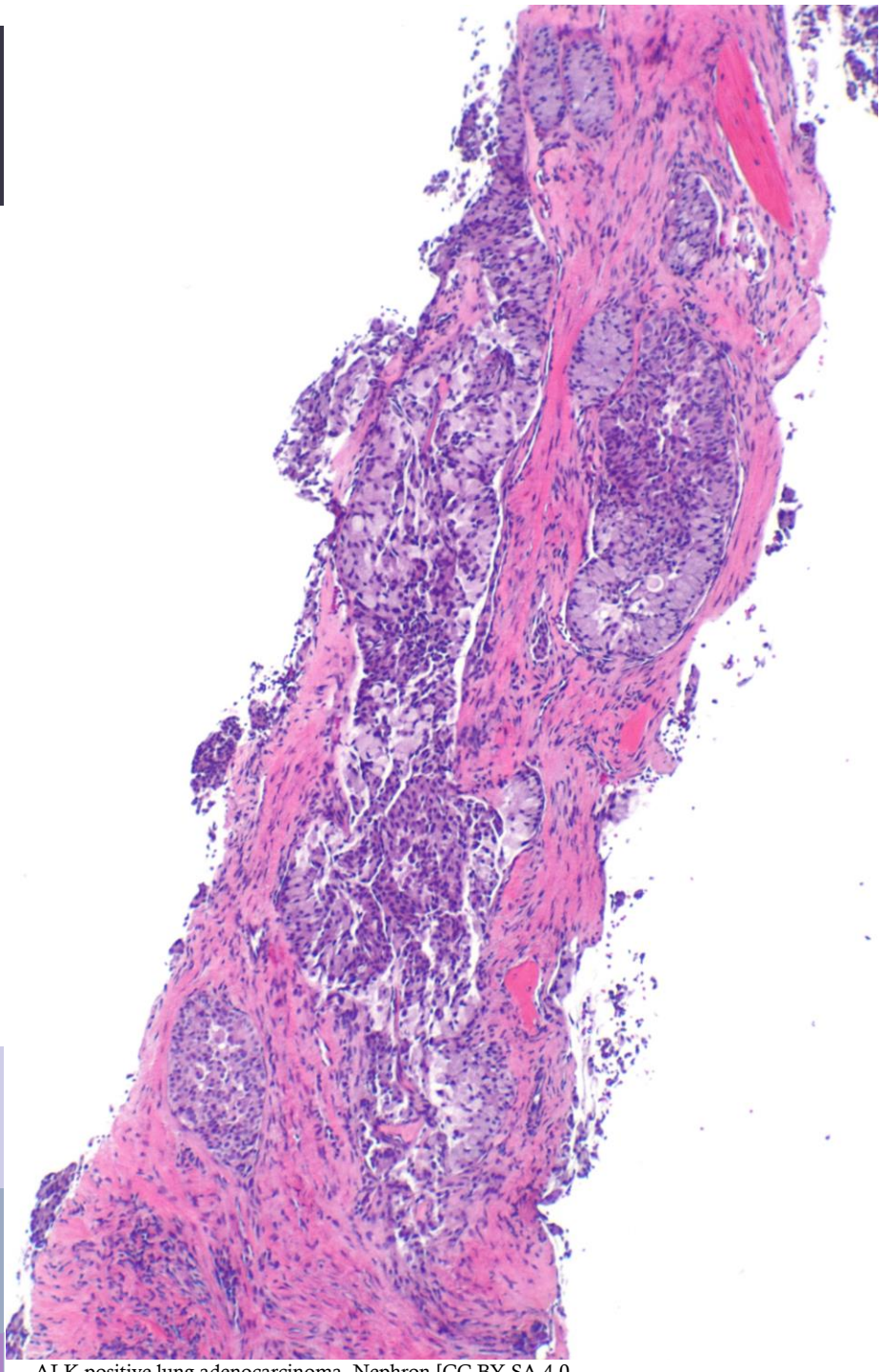
ALKFUSION



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

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Intra-Cranial Efficacy of Brigatinib in an ALK-Positive Non-Small Cell Lung Cancer Patient Presenting Leptomeningeal Carcinomatosis

"Our case provides additional data on brigatinib's intracranial activity, not only on brain metastasis but also on leptomeningeal disease, after experiencing resistance to both crizotinib and ceretinib, 1st and 2nd generation ALK inhibitors."

The Incidence of ALK Inhibitor-Related Pneumonitis in Advanced Non-Small-Cell Lung Cancer Patients: A Systematic Review and Meta-Analysis

"The overall incidence of ALK inhibitor pneumonitis was 2.14% in patients with advanced NSCLS. The patients from Japanese cohorts had a higher incidence of ALK-inhibitor pneumonitis, which indicates the need for increased awareness and caution for pneumonitis in Japanese patients treated with ALK inhibitors."

Brigatinib: New-Generation ALK Inhibitor for Nonsmall Cell Lung Cancer

"In several clinical trials, brigatinib has exhibited significant improvement in progression-free survival in patients that have experienced resistance to crizotinib therapy."

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

"Liquid biopsy of CSF 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. Thus, CSF might be promising as a medium of liquid biopsy in LM."

Meta-Analysis Comparing Incidence of Grade 3–4 Neutropenia with ALK Inhibitors and Chemotherapy in Patients with Non-Small-Cell Lung Cancer

"In patients with non-small-cell lung cancer, incidence of grade 3–4 neutropenia with ALK-targeted therapy is not significantly different compared with chemotherapy."

A Study of ALK-Positive Pulmonary Squamous-Cell Carcinoma: From Diagnostic Methodologies to Clinical Efficacy

"The positive concordance rate of ALK IHC (immunohistochemistry) and FISH (fluorescence in-situ hybridization) in LSCC (lung squamous-cell carcinoma) is far less than that reported for LADC (lung adenocarcinoma). Therefore, ALK IHC detection in LSCC cannot be used as a diagnostic method for ALK rearrangement."

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."

ASCO 2019 ALK-RELATED ABSTRACTS

Below are ALK-related abstracts that were released in the upcoming ASCO 2019 Conference. Stay tuned for more updates on ASCO presentations on Twitter and on our Facebook page.

Efficacy of Platinum-Pemetrexed Combination Chemotherapy in ALK+Non-Small Cell Lung Cancer Refractory to Second-Generation ALK TKIs

"Here we evaluate the efficacy of PT/pemetrexed (pem)-based chemo in pts with ALK+ NSCLC refractory to second-gen TKIs… [In this retrospective study,] [t]he efficacy of PT-pem-based chemo is limited after failure of second-gen ALK TKIs but may be higher in pts who receive chemo plus ALK TKI, suggesting a potential role for ongoing ALK inhibition. The modest benefit of PT-pem-based chemo highlights the need for other therapeutic strategies for pts refractory to second-gen TKIs."

ALK Resistance Mutations and Co-occurring Genetic Alterations to the ALK Tyrosine Kinase Inhibitors in Lung Cancer

"Using targeted gene capture and next-generation sequencing technologies, we analyzed the somatic mutations from174 patients (pts) with post-TKI samples….In lung cancer patients, *ALK* resistance point mutations G1269A was significantly enriched in post-crizotinib, while patients with multiple ALK-TKIs may frequently found G1202R or L1196M. The co-occurring genetic alterations in *TP53* or *EGFR* after the TKIs therapeutic may offer directions for further research and therapy in lung cancer."

The Role of Low Dose Aspirin, Vitamin D, or Metformin in EGFR, ALK, and ROS Positive Non-small Cell Lung Cancer: A Single Institution Retrospective Analysis

"Patients (pts) with EGFR, ALK, ROS pos NSCLC treated with first line TKI from January 2014 to June 2017 were included. Information on concurrent use of MAD was obtained. [MAD is Metformin, Aspirin and Vitamin D]… To our knowledge, no data has been published regarding use of MAD in NSCLC with driver mutations. In our study, concurrent use of vitamin D with TKI prolonged PFS in these pts. However, this effect was not seen with metformin or aspirin. Our study was limited by retrospective design, possible under-reporting of medication use by patients and small patient population."

Cross-Sectional Imaging Utilization for EGFR, EML/ALK, and KRAS Mutant on-Small Cell Lung Cancer

"Mean duration between date of diagnosis and death for each group was 1099 ± 770 days (EGFR), 1139 ± 924 days (EML/ALK), and 542 ± 602 days (KRAS). Compared to the KRAS group, the EML/ALK group had higher utilization of chest CTs ($p = 0.044$), pulmonary embolus CTs ($p = < 0.001$), abdominopelvic CTs ($p = 0.004$), and PET CTs ($p = 0.006$). The EGFR group had significantly fewer pulmonary embolus CTs ($p = < 0.001$) and higher numbers of non-brain MRIs ($p = 0.004$) compared to the KRAS group, as well as fewer abdominopelvic CTs ($p = 0.034$) compared to the EML/ALK group."

Longitudinal Analysis of Plasma ALK Mutations During Treatment with Next-Generation ALK inhibitors

"To assess the evolution of *ALK* muts during treatment with different TKIs, we analyzed serial plasma specimens from 20 pts treated with sequential 2nd-gen/2nd-gen or 2nd-gen/3rd-gen TKIs. Among six pts who received alectinib followed by brigatinib, repeat plasma analysis at brigatinib progression revealed persistence of pre-brigatinib *ALK* muts in two pts (one L1196M and one G1202R), expansion of G1202R in one pt, and acquisition of new *ALK* muts in three pts. Among 14 pts who received a 2nd-gen TKI followed by lorlatinib, 11 had persistence of pre-lorlatinib *ALK* muts and 8 acquired ≥1 additional *ALK* muts at lorlatinib progression. The most frequently acquired *ALK* mut was D1203N in four of eight cases. *ALK* resistance muts are prevalent at relapse on next-generation ALK TKIs and increase with each successive generation of ALK TKIs. These findings suggest that sequential therapy with increasingly potent ALK TKIs may select for compound *ALK* muts and/or fuel tumor heterogeneity."

Effect of Concurrent TP53 Mutation in EGFR/ALK/ROS1 Positive Non-small Cell Lung Cancer Treated with First-line TKI Therapy: A Single Institution Retrospective Study

"We conducted a retrospective study to determine the impact of concurrent TP53 mutation (TP53m) in this [the EGFR and ALK] population…. in our study, although there was a tendency towards improved survival and delayed TKIr in the cohort without TP53m, it was not statistically significant, which may be due to small sample size. Further studies looking at concurrent TP53m and targetable mutation are required, which may help clinicians deciding how to direct therapy in this population."

Preliminary Results of Single Arm Phase 2 Trial of Brigatinib in Patients (pts) with Progression Disease (PD) After Next-generation (NG) Anaplastic Lymphoma Kinase (ALK) Tyrosine Kinase Inhibitors (TKIs) in *ALK*+ Non-small Cell Lung Cancer (NSCLC)

"Between 3/2017 and 11/2018, 20 pts were enrolled in the [brigatinib trial post second generation TKI]. Pt characteristics were: median age 55 years (range 32 to 71), median number of prior therapies 3 (range 1 to 6), 12 had CNS disease at the baseline (8 pts had CNS PD). *ALK* resistance mutation detected in 3 of 8 pts on standard of care molecular testing. ORR results were confirmed partial response (n = 8), stable disease (n = 7), PD (n = 3), unconfirmed response (n = 1), and non-evaluable due adverse events (AE's) (n = 1) ….Brigatinib has activity after progression on next generation ALK TKI."

Efficacy and Safety of Crizotinib in Patients with ALK Positive Non small Cell Lung Cancer (NSCLC): Real-World Findings

"Fifty-eight patients with NSCLC ALK+ were recollected, 33 women and 25 men. The median age was 61 years (25-88); 46.6% were never smokers, 31% were former smokers. The majority (96.6%) had confirmed adenocarcinoma histology and 25.9% had brain metastases at initial treatment. Crizotinib was used as first line 55.2% and second line in 37.9%. Progression disease was the most frequent reason of discontinuation of crizotinib (74%) and in 5 patients was discontinued because of toxicity. The most frequent toxicities were edemas (37.9%), increased transaminases (27.5), diarrhea (24%) and nauseas (20%). Grade 3-4 toxicities were present in 4 cases with increase transaminases, 1 case of neumonitis and 2 patients with diarrhea. The response rate was 63.8%. The median PFS was 12.66 months (95% CI :7.95-17.38) and median OS was 23.36 months (95%CI: 16.29-30.44).In patients with brain metastases (15) the response rate was 46.6% and median OS decrease to 15.36 months (95%CI: 0.1-30.8). Conclusions: Our findings indicate that the results of crizotinib in the real world are consistent or slightly improved with prior clinical trial in PFS and OS, despite our sample includes patients for first line and second/later line crizotinib and ¼ of patients had brain metastasic at crizotinib initiation."

Economic Evaluation of Anaplastic Lymphoma Kinase (ALK) Inhibitors Brigatinib, Alectinib and Crizotinib in Non-small Cell Lung Cancer (NSCLC): Analysis for Intracranial Metastasis-Related Progression Free Survival (CNSPFS)

"This independent economic evaluation suggests that, despite the lower costs of per-label alectinib and crizotinib, greater gains in CNSPFS Lys [CNS Progression Free Survival Life Years] and QALYs [Qualify Adjusted Life Years] are achieved with per-label brigatinib in the setting of CNS metastasis. This assumes willingness to pay thresholds up to $1,152,445/CNSPFS LY and up to $1,198,025/CNSPFS QALY gained, which is above prevailing standards."

Final PFS Analysis and Safety Data From the Phase III J-ALEX Study of Alectinib (ALC) vs. Crizotinib (CRZ) in ALK-inhibitor Naïve ALK-positive Non-small Cell Lung Cancer (ALK+ NSCLC)

The final PFS HR was 0.37 (95%CI 0.26-0.52): median IRF-PFS [Independent Review Facility Progression Free Survival] was 34.1 months (95%CI 22.1– not estimated) in the ALC arm and 10.2 months (95%CI 8.3–12.0) in the CRZ arm. HRs for the time to CNS progression or death was 0.33 (95%CI 0.11–0.93) and 0.20 (95%CI 0.08–0.49) with or without CNS metastases at baseline, respectively."

Health-related Quality of Life (HRQoL) Results from ALTA-1L: Phase 3 Study of Brigatinib vs Crizotinib as First-line (1L) ALK therapy in Advanced ALK+ Non-small Cell Lung Cancer (NSCLC)

"Consistent with the prolongation of PFS seen in 1L treatment of advanced ALK+ NSCLC, brigatinib improved HRQoL [Health related quality of life] and prolonged the duration of improvement in GHS/QoL, [Global Health Status] and the majority of functional and symptom domains vs crizotinib."

Association of PFS with Levels of Pretreatment Lactate Dehydrogenase in Patients with EML4-ALK Rearrangement Non-small Cell Lung Cancer Treated with ALK Tyrosine Kinase Inhibitor

"We performed a retrospective analysis to investigate the association between the lactate dehydrogenase (LDH) levels and progression-free survival (PFS) in patients with echinoderm microtubule-associated protein-like 4-anaplasticlymphoma kinase (EML4-ALK) rearrangement non-small cell lung cancer (NSCLC) receiving treatment with crizotinib… An elevated pre-treatment serum LDH level (> 250U/L) is significantly associated with shorter PFS in patients with EML4-ALK rearrangement NSCLC. Post-treatment elevated serum LDH level is associated with multiple factors including muscle damage and anemia, rather than PFS."

Circulating Free DNA as a Prognostic Biomarker in Patients with Advanced *ALK*+ NSCLC Treated with Alectinib from the Global Phase III ALEX Trial

"Tumor burden positively correlated with cfDNA amount; patients with ≤median cfDNA at baseline had better prognosis than those with > median cfDNA. Alectinib consistently improved PFS, DOR and ORR versus crizotinib across BEPs [Biomarker-evaluable populations], reducing the risk of tumor progression by > 50% compared with crizotinib."

Early Circulating Tumor (Ct)DNA Dynamics and Efficacy of Lorlatinib in Patients (pts) with Advanced ALK-Positive Non-small Cell Lung Cancer (NSCLC)

"Early ctDNA dynamics may predict lorlatinib efficacy in *ALK*$^{+}$ NSCLC, with decreased ctDNA at 6 wks associated with better response and longer PFS. Further studies are needed to validate these findings and to determine whether early intervention based on dynamic ctDNA monitoring may improve outcome."

Efficacy of Tyrosine Kinase Inhibitors (TKIs) Based on the ALK Resistance Mutations on Amplicon-Based Liquid Biopsy in ALK Positive Non-small Cell Lung Cancer (NSCLC) Patients (pts)

"The absence of ctDNA mutations at TKI failure was associated with prolonged OS, whereas complex *ALK* mutations at TKI failure may predict resistance to subsequent therapy. Larger and specifically designed studies should be performed to validate these findings."

The Efficacy of Immune Checkpoint Inhibitors and PD-L1 Status in Patients with Advanced Non-small Cell Lung Cancer Harboring Oncogenic Driver Alterations: Immuno-oncology Biomarker Study in LC-SCRUM-Japan.

"The efficacy of immune checkpoint inhibitors (ICI) and PD-L1 status in patients with advanced non-small cell lung cancer (NSCLC) harboring oncogenic alterations has not been fully investigated. We initiated this immuno-oncology biomarker study as part of nationwide genomic screening by LC-SCRUM-Japan (LC-SCRUM-IBIS)….Among 9 responders to ICI, 3 had KRAS, 2 had MET and 1 each had ALK/EGFR/HER2/RET….PD-L1 status seemed to vary among patients with advanced NSCLC harboring oncogenic alterations. New biomarker for ICI therapy in this population should be moreover explored."

Brigatinib (BRG) versus Crizotinib (CRZ) in Asian versus non-Asian patients (pts) in the Phase III ALTA-1L Trial

"[Brigatinib] showed comparable improvement in PFS vs [crizotinib] both in Asians and non-Asians in ALK inhibitor–naive ALK+ NSCLC."

Matching Insurance Claims Data with EMR Molecular Status Data in Non-small Cell Lung Cancer (NSCLC) Patients: Understanding Real-World Molecular Testing and Prevalence Rates at the Site and Investigator Level

"US insurance claims data were extracted to identify lung cancer patients. These data were matched with EMR data also containing NSCLC patients' details regarding the occurrence and results of molecular testing for EGFR, ALK, ROS1, JAK2, HER2 and RET somatic alterations, achieving a level of granular detail beyond that available in each individual dataset. A one-year extraction period was applied, with no gender or age restrictions….The observed prevalence correlated reasonably well with literature reported prevalence for the molecular biomarkers associated commercially available targeted therapies in NSCLC (EGFR, ALK, ROS1)."

The Impact of Sequential Therapy of Crizotinib Followed by Alectinib: Real-World Data Analysis of 840 ALK-inhibitor Naïve Patients with NSCLC Harboring ALK-Rearrangement (WJOG9516L)

"We reviewed the clinical data of ALK-rearranged NSCLC patients who received CRZ or ALEC between May 2012 and Dec 2016. Patients were divided into two groups according to the first-administered ALK inhibitor, the CRZ or ALEC group. In order to evaluate the efficacy of the sequential strategy of "CRZ followed by ALEC", the combined time to treatment failure (TTF) was calculated in the CRZ group as defined by the sum of the "TTF of CRZ" plus the "TTF of ALEC" if patients were treated with ALEC followed by CRZ. In the ALEC group, the "TTF of ALEC" was calculated. The primary endpoint is the comparison between the combined TTF in the CRZ group with the TTF in the ALEC group. …The combined TTF [time to treatment failure] 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."

Brigatinib in Pretreated Patients with ALK-positive Advanced NSCLC

"This retrospective multicentric study analyzed ALK-+ advanced NSCLC patients pretreated with at least two tyrosine-kinase inhibitors, including crizotinib, and enrolled in the brigatinib French early access program. The primary endpoint was investigator-assessed progression-free survival (PFS). Results: 104 patients were included (mean age, 56.6 years; never smokers, 61.5%; adenocarcinoma, 98.1%). Patients had received a median of 3 previous treatment lines, including at least 2 ALK inhibitors, mainly crizotinib then ceritinib in 93% patients. At brigatinib initiation, 59.1% had performance status 0-1, 51.9% had ≥ 3 metastatic sites, 74.5% had central nervous system metastases (CNS) and 8.8% had carcinomatous meningitis. Median duration of brigatinib treatment was 6.7 (0.06–20.7) months. Median PFS was 6.6 (95% CI, 4.8–9.9) months for the entire population. In the 91 evaluable patients, disease control rate was 78.2% (stable, 28.2%; partial response, 45.7%; complete response, 4.3%). From brigatinib start, median overall survival was 17.2 (95% CI:11.0–not reached) months."

Prevalence of Targetable Mutations in Black Patients with Lung Cancer: A Systematic Review and Meta-Analysis

According to this retrospective analysis, 1% of blacks have the ALK transfusion.

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