Emergence of KRAS mosaicism with multiple variants during treatment with alectinib in ALK-positive metastatic non-small cell lung cancer: A case report

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Abstract. *ALK* fusions occur in 3-6% of lung cancers and confer sensitivity to ALK-tyrosine kinase inhibitors. However, acquired resistance inevitably develops through multiple mechanisms, limiting the durability of the treatment response. The present report describes the case of a 36-year-old man with *ALK*-rearranged lung adenocarcinoma treated with the second-generation ALK-tyrosine kinase inhibitor alectinib. At the time of disease progression, molecular analysis revealed the emergence of a *KRAS* mosaicism. The present report details the molecular evolution of the tumor, from the initial diagnosis to treatment failure. The current report illustrates a compelling mechanism of resistance to ALK inhibition driven by the synchronous emergence of multiple *KRAS* variants. While previous case reports have documented an isolated *KRAS* mutation as a potential resistance mechanism to ALK-tyrosine kinase inhibitor therapy, to the best of our knowledge, this is the first report describing such extensive KRAS mosaicism upon failure of alectinib treatment. The present report highlights the importance of reevaluating the molecular profile of the cancer at the time of progression to accurately define the resistance pathway and develop rational therapeutic strategies capable of overcoming this resistance.

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Abbreviations: NSCLC, non-small cell lung cancer; PFS, progression-free survival; CT, computed tomography; PET, positron emission tomography; RNASeq, RNA-sequencing; DNASeq, DNA-sequencing; CNV, copy number variation

Key words: ALK rearrangement, next-generation sequencing, KRAS mutation, liquid biopsy, NSCLC

Introduction

Oncogene-addicted lung cancer typically affects young patients without a history of tobacco exposure. In metastatic non-small cell lung cancers (NSCLC), molecular diagnosis is recommended for treatment decisions. Anaplastic lymphoma kinase (*ALK)* gene fusions are observed in 3-6% of NSCLC (1) and are associated with increased tumor cell proliferation and survival properties. About 90 different fusion partners have been described for *ALK* gene (2), Echinoderm microtubule-associated protein-like 4 (EML4)-*ALK* gene fusions represent the most frequent *ALK* rearrangement (accounting for 85% of *ALK* rearrangements) (3). These fusions confer sensitivity to ALK kinase inhibitors such as crizotinib, alectinib, ceritinib, brigatinib, lorlatinib or ensartinib (4,5). Treatment with alectinib has been associated with a prolonged progression-free survival (PFS) of 48.2 months in the first-line setting, establishing it as a recommended option (6). However, based on the CROWN study, which reported a 60% PFS rate at 5 years, lorlatinib is now considered the preferred first-line treatment (7). During anti-ALK treatment, acquired resistance mechanisms inevitably occur. Liquid biopsy represents an attractive and non-invasive alternative to tissue biopsy for resistance mutations identification or switch treatment (8).

Here, we report the case of a 36-year-old man with an *ALK*-positive metastatic NSCLC, which develops six different *Kirsten rat sarcoma virus (KRAS)* mutations at progression after treatment with alectinib.

Case report

A 36-year-old, never-smoker, Caucasian male presented to the emergency department of Nancy's university hospital in France (CHRU de Nancy) in September 2023, with symptoms of dyspnea, cough, and lateral thoracic pain persisting for five weeks. He had no significant medical history or treatment and was an active sportsman. There was no known exposure to asbestos.

A computed tomography (CT) scan revealed two masses in the left upper lobe, measuring 22 and 46 mm, associated with a tumor infiltration in the right perihilar region, encasing the right main bronchus, and in the left hilar region, encasing the right pulmonary artery and right pulmonary veins. Multiple mediastinal lymphadenopathies and a suspicious left adrenal nodule were also identified. Magnetic resonance imaging of the head revealed two brain metastases of 4 and 5 mm. A positron emission tomography (^{18}FDG-PET scan) scan revealed hyperfixation in the right upper lobe mass (Fig. 1A), and several nodules in the left lung, the hilar regions, and the right lower and middle lobes, associated with a minor right pleural effusion. Bilateral supraclavicular and mediastinal lymphadenopathies were also observed, along with hyperfixation in the left adrenal gland. Bronchoscopy identified a tumoral infiltration in the right lower and middle lobes (Fig. 1B). Ten biopsies were collected for anatomopathological examination. The pathologist diagnosed a non-small cell lung adenocarcinoma. Immunohistochemical staining showed ALK expression in 80% of the tumor cells, and Programmed death-ligand 1 (PD-L1) expression in 60% of the tumor cells, ROS1 expression was negative (Fig. 2).

Molecular diagnosis first included the research of hotspots *EGFR* variants using Idylla® *EGFR* mutation assay (Biocartis, Mechelen, Belgium) on formalin-fixed and paraffin-embedded tumor sample. This PCR-based assay did not detect any mutation in the *EGFR* gene. RNA-based sequencing (RNASeq) was then performed but provided uninterpretable results due to the low quality of RNA extracted from the sample. A liquid biopsy sample was collected a few days later and targeted 51-gene DNA-based sequencing (DNASeq, custom Solid Tumor Solution, Sophia Genetics, Saint Sulpice, Switzerland) (9), it revealed a pathogenic c.524G>A R175H *TP53* gene mutation (NM_000546.6) with an 7.2% allele frequency (AF) and copy number variations (CNV) in the *KRAS* gene (CNV value of 8.5). To confirm the presence of *ALK* rearrangement as suspected by immunohistochemistry, another bronchoscopy was conducted, and eight novel biopsies were obtained. Analysis of these biopsies by RNASeq revealed a rearrangement between *EML4* (exon 13) and *ALK* (exon 20) genes, ALK (NM_0043304.5), fusion breakpoints: chr2:42522656; chr2:29446394, AF: 97%).

Based on this, treatment with alectinib (600 mg daily) was initiated, following national guidelines for ALK-NSCLC as first line therapy at that time Based on these findings, first-line treatment with alectinib (600 mg twice daily) was initiated, in accordance with the French national guidelines (IFCT, January 2023 version) (10) and the European Society for Medical Oncology (ESMO) 2023 clinical practice guidelines (4) for ALK-rearranged NSCLC. At the 1-month clinical evaluation, an improvement in dyspnea, cough, and general health status was observed. However, the patient exhibited biological adverse events in the first four months of treatment, including grade-2 hyperbilirubinemia, and grade-1 creatine phosphokinase increase. After 3 months of treatment, he had a complete resolution of dyspnea and cough but presented a grade-1 asthenia. A ^{18}FDG-PET scan performed 3 months after treatment initiation revealed regression of all pulmonary and adrenal lesions (Fig. 3A).

The ^{18}FDG-PET scan, performed 7 months after the initiation of alectinib, revealed disease progression, with increase in size of known bilateral pulmonary nodules and eight novel pulmonary lesions (Fig. 3B). The thoracic tumor board confirmed disease progression and recommended switching from alectinib to lorlatinib. The analysis by DNASeq of a second liquid biopsy collected at the time of treatment switch detected the known R175H *TP53* variant as well as six novels pathogenic *KRAS* variants (L19F, G12V, G12D, G13C, and G12C variants with AF ranging from 2 to 3% and Q61H variant at 23.3% AF). Copy number gain of the *KRAS* gene was also detected (CNV value: 3). One month later, another liquid biopsy was collected and analyzed by a new approach named Hedera Profiling 2 ctDNA panel (Hedera Dx, Epalinges, Switzerland) which allows the detection of both single nucleotide variations, CNV, microsatellite instability, and specific gene fusions in 32 genes of interest. This technique confirmed the presence of the *TP53* and *KRAS* genes variants with no *ALK* rearrangement.

Following a 7-day washout period after the last dose of alectinib, the patientinitiated treatment with second-line lorlatinib (100 mg daily). This therapeutic strategy was administered as standard-of-care therapy, based on the clinical evidence established by the CROWN trial (7) and in accordance with the IFCT-2023 (10) and ESMO-2023 (4) guidelines for ALK-positive NSCLC. The lorlatinib dosage was set at 100 mg daily. At this time, the patient experienced symptoms of dyspnea, cough, and mild hemoptysis. He presented under treatment an adverse event of depressive mood, which resolved spontaneously after a few weeks. The patient also presented hypercholesterolemia, treated with rosuvastatin.

A follow-up CT scan was performed 3 months after lorlatinib initiation, it detected multiple progression in the lungs and adenopathies (Fig. 3C). Therefore, a bronchoscopy was performed and culmen biopsies were obtained for DNASeq and RNASeq analyses. We retrieved one known *KRAS* mutation (G13C, 28.7% AF), one known *TP53* mutation (R175H, 14% AF) and the *EML4* (exon 13)*::ALK* (exon 20) rearrangement (AF 91%) associated with *KRAS copy number gain* (CNV value: 9.1). A phylogenetic tree resuming genetic evolution can be found in Fig. 4. A switch to chemo-immunotherapy was then decided, before resistance to targeted therapy and multiple resistance genetic alterations, following national guidelines for first line immunochemotherapy for NSCLC. The patient passed away in March 2025 due to disease progression.

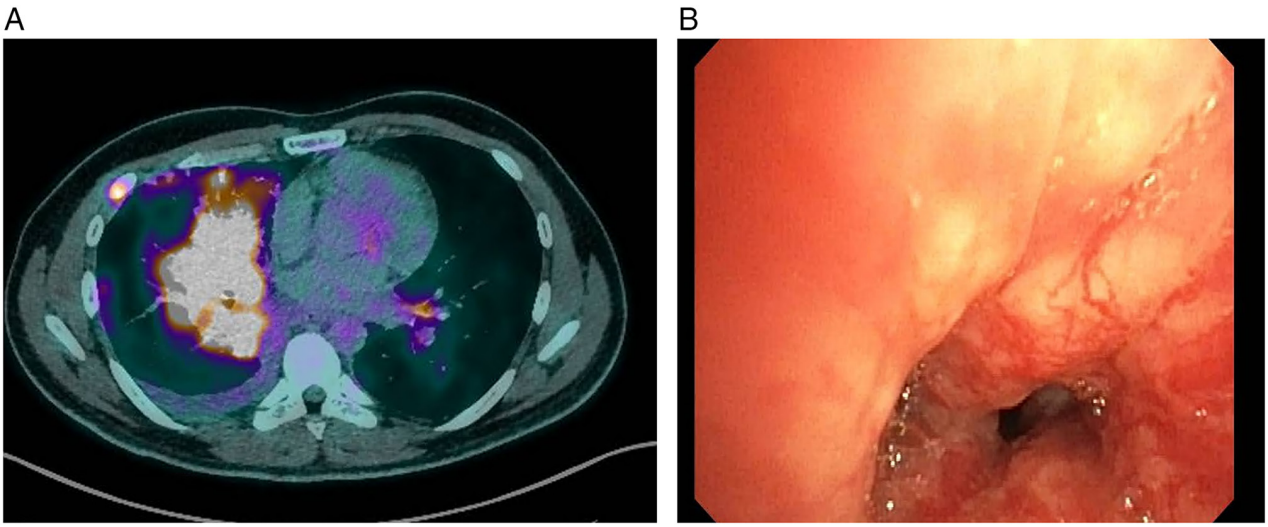

Figure 1. PET scan and bronchoscopy images at diagnosis. (A) PET scan showing hypermetabolism of the right hilar mass. ^{18}F-fluorodeoxyglucose-PET/computed tomography fused transversal images were acquired after 6-h fasting. (B) Bronchoscopy image showing a mass in the culmen. Biopsies were obtained through flexible bronchoscopy performed with a bronchoscope under sedation. The procedure included the visualization of massive infiltration of the right bronchial tree, with collection of 10 biopsies for histopathologic examination and theranostic marker assessment. PET, positron emission tomography.

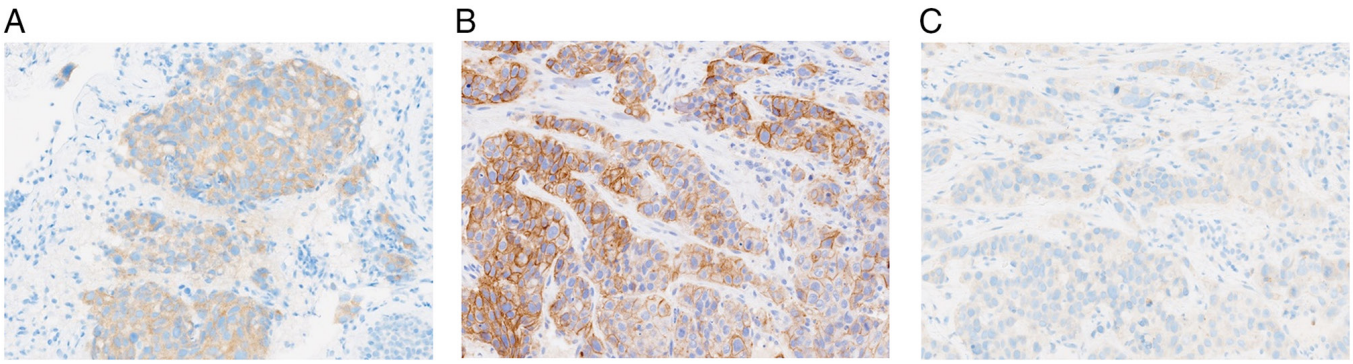

Figure 2. ALK, PD-L1 and ROS1 immunohistochemistry images. (A) ALK expression was assessed by immunohistochemistry. Moderate granular cytoplasm staining was observed for ALK, with a score of 2+ (magnification, x200). The fixative used was 10% buffered formalin. Immunohistochemistry was performed using the VENTANA Benchmark automated platform (Roche Tissue Diagnostics). Anti-ALK antibody (clone 5A4; Abcam) was diluted at 1:100. Antigen retrieval was performed using CC1 for 32 min. The duration of incubation with primary antibody was 1 h. Detection was performed using OptiView DAB. (B) PD-L1 expression was assessed by immunohistochemistry. Diffuse membrane staining was observed for PD-L1 (tumor proportion score, 80%; magnification, x200). The fixative used was 10% buffered formalin. Immunohistochemistry was performed using an Agilent OMNIS automated platform (Agilent Technologies, Inc.). PD-L1 antibody (prediluted; clone 22C3; Agilent Technologies, Inc.) was used. Antigen retrieval was performed under low pH conditions for 40 min. The duration of incubation with primary antibody was 40 min. Detection was performed using EnVision FLEX+Mouse DAB Enhancer. (C) ROS1 expression was examined using immunohistochemistry. Weak cytoplasm and membrane staining was observed for ROS1, with a score of 1+ (magnification, x200). The fixative used was 10% buffered formalin. Immunohistochemistry was performed using the VENTANA Benchmark automated platform. Anti-ROS1 antibody (SP384; ready to use) was used. Antigen retrieval was performed using CC1 for 64 min. The duration of incubation with primary antibody was 16 min. Detection was performed using OptiView DAB. ALK, anaplastic lymphoma kinase; CC1, Cell Conditioning 1; DAB, 3,3'-diaminobenzidine; PD-L1, programmed death-ligand 1.

Discussion

Our case depicts a real-life resistance to alectinib used in the first-line setting for a patient with *ALK*+ NSCLC. It highlights the importance of reevaluating the tumor's molecular characteristics at clinical progression as resistance mutations can occur during treatment. Various mechanisms have been explored to explain acquired resistance to ALK inhibition. Gainor *et al* (11) studied resistance mechanisms in 103 *ALK*+ NSCLC patients and found that the most frequent resistance mechanism to second-generation ALK inhibitors was the emergence of secondary *ALK* mutations, especially the G1202R variant, they did not report any *KRAS* mutations in their cohort. Lin *et al* (12) confirmed their findings in their 25-patient population. A review from Toyokawa and Seto evaluated the resistance mechanisms to crizotinib, alectinib, and ceritinib (13), showing that a mutation or a copy number gain in the *ALK* gene, or the reactivation of bypass tracks (including *KRAS* variants) could explain resistance. They found three cases of patients presenting resistance to crizotinib due to *KRAS* mutation, with one presenting a primary resistance due to co-occurring *ALK* and *KRAS* alterations at diagnosis.

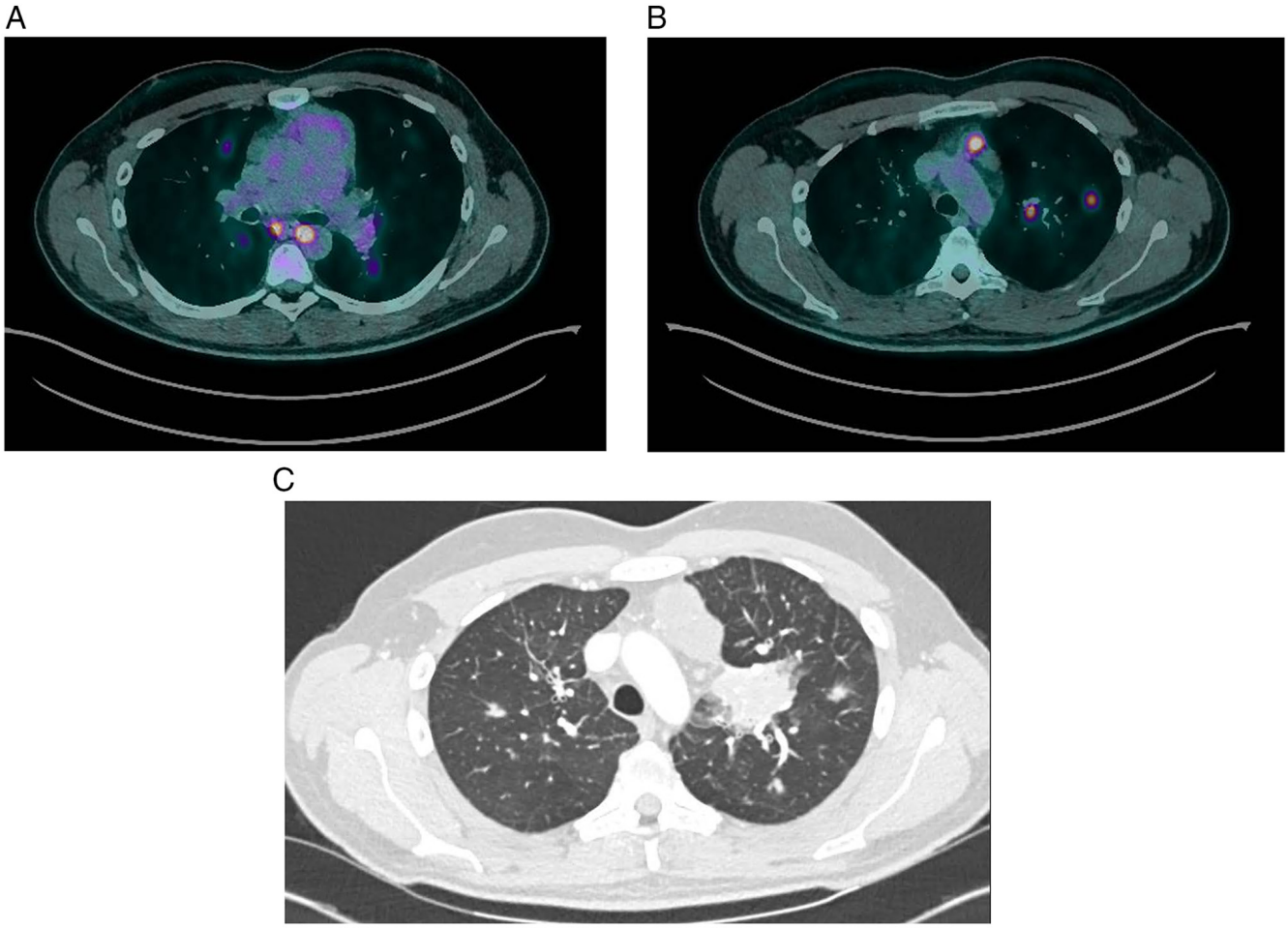

Figure 3. Radiological evidence of therapeutic response and subsequent disease progression. (A) Partial metabolic response (3 months of alectinib treatment): PET-CT axial slice at the hilar level showing near-complete disappearance of the previously described hypermetabolic right hilar mass (compared with Fig. 1A). (B) Disease progression (7 months of alectinib treatment): PET-CT axial slice at the level of the aortic arch revealing multiple new hypermetabolic foci, including bilateral pulmonary nodules and anterior mediastinal lymphadenopathy. (C) Further progression (3 months of lorlatinib treatment): Follow-up CT scan (lung window) at the level of the aortic arch showing an increase in size of the left hilar mass and development of multiple bilateral pulmonary nodules. CT, computed tomography; PET, positron emission tomography.

The emergence of *KRAS* mutations as a resistance mechanism is biologically plausible, as they activate the MAPK/ERK signaling pathway downstream of the ALK receptor, inducing cancer progression independently of the ALK pathway (13). Other clinical cases reported *KRAS* mutations as a resistance mechanism to *ALK* inhibitors in *ALK*+ NSCLC, often showing initial responses followed by rapid progression (14-21). In these previous reports, patients were usually treated with crizotinib, a first-generation *ALK* inhibitor, and presented with a *KRAS* mutation at progression, or at diagnosis with primary resistance. Progression usually occurred within 1 to 3 months, but in three cases out of 21, it happened after 6 months of treatment. To our knowledge, we described here for the first time the emergence of multiple *KRAS* mutations in a single case.

Although specific mutations (G12C, Q22K, G12V, G13D, A146V and Q61H) have been observed, this case is, to our knowledge, the first to describe extensive *KRAS* mosaicism under anti-ALK treatment. The technical validity of these findings is supported by the high Variant Allele Frequency (VAF) of the Q61H mutation (23.3%) detected at progression. This high VAF, combined with the use of Unique Molecular Identifiers (UMIs) in our liquid biopsy assays (limit of detection, LOD, 0.5%), allows us to exclude laboratory artifacts [detailed technical specifications of the NGS platforms and gene panels are provided in Data S1 and Tables SI-III, and detailed mapping of the five primary datasets (SRX31979634 to SRX31979638) according to sample type and collection date is provided in Table SIV] (9,22,23). Regarding the timing of these alterations, our case suggests a dual resistance process. While the *KRAS* amplification and *TP53* mutation present at diagnosis likely acted as primary resistance factors contributing to a reduced initial sensitivity, the *KRAS* mosaicism was not detectable at baseline even with high-sensitivity NGS analysis (LOD 0.5%). This supports the hypothesis that these specific *KRAS* variants were acquired or selected under the selective pressure of alectinib, driving progression as an acquired bypass mechanism.

Hua *et al* (24) described a potential resistance mechanism to ALK inhibitor mediated by *KRAS* amplification in one of their cases. In our case, the patient presented *KRAS* amplification at diagnosis, which may have contributed to resistance to both ALK inhibitors. An interesting piece of information

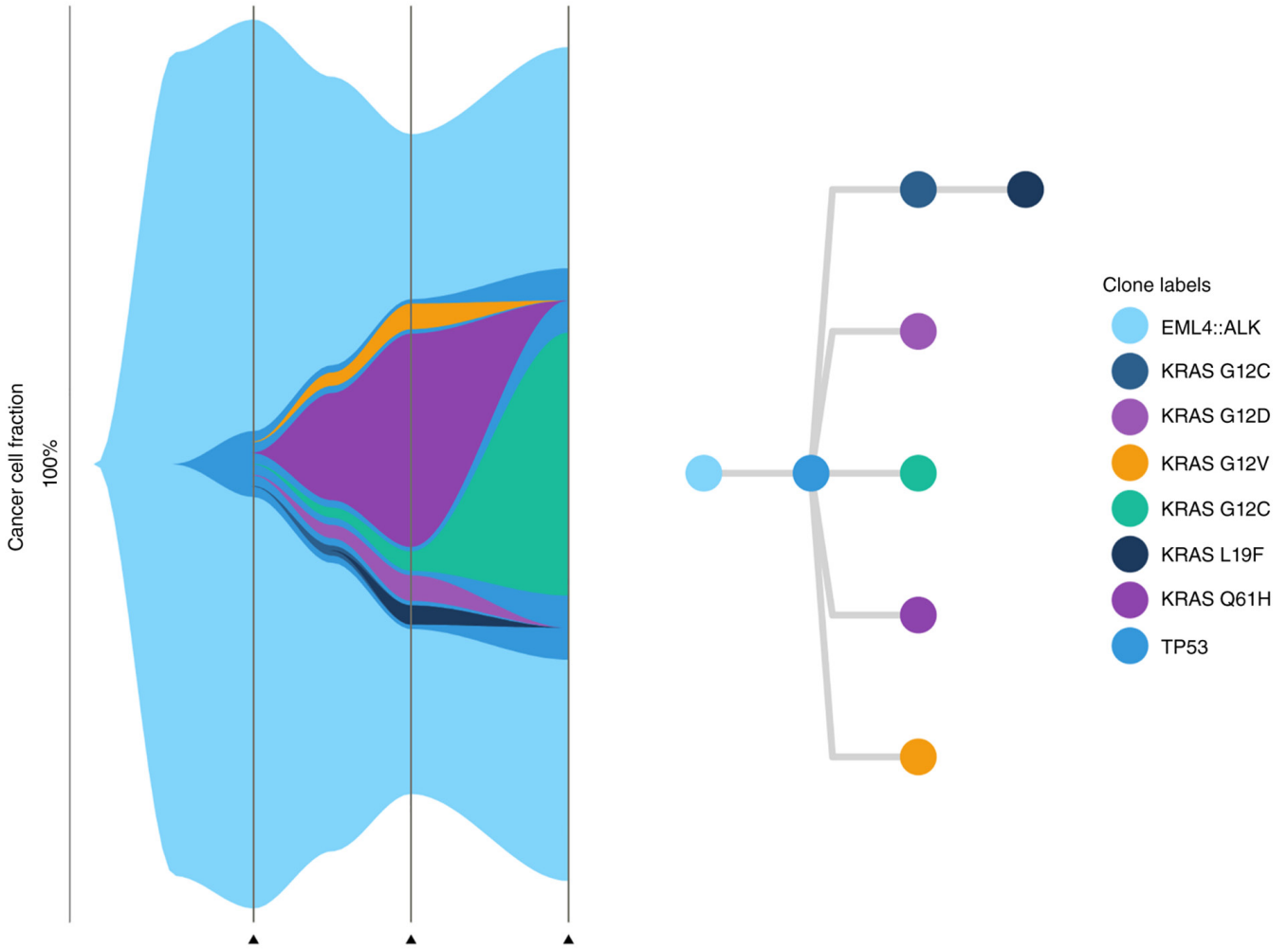

Figure 4. Phylogenetic tree illustrating the evolution of genetic mutations in the patient's cancer: Hypotheses on divergent clonal lineages based on next-generation sequencing results. The allele frequencies were: i) At diagnosis (second vertical bar): TP53, 7.2%; EML4::ALK, 97.0%; ii) at first progression (third vertical bar): KRAS L19F, 2.1%; KRAS G12C, 2.1%; KRAS G12V, 2.8%; KRAS G12D, 2.8%; KRAS G13C, 2.1%; KRAS Q61H, 23.3%; TP53, 2.9%; and iii) at second progression (fourth vertical bar): KRAS G13C, 28.7%; TP53, 14.0%; EML4::ALK, 91.0%. The figure was generated using the ClevRvis package (v.1.8.0; https://github.com/sandmanns/clevRvis) and R (v.4.3.1; R Core Team; https://www.r-project.org/). ctDNA, circulating tumour DNA.

is the reevaluation of the *EML4::ALK* fusion, which was not found at first progression. Gainor *et al* (11) stated that *ALK* fusion and *KRAS* mutation could not coexist; however, our case report clearly demonstrates the contrary, joining other reports of concomitant *ALK* rearrangements and *KRAS* mutations (16-19,25,26). This discrepancy could be explained by tumor heterogeneity, as suggested by Tang *et al* (27). This evolution illustrates that the molecular profile is not static; a selection process eliminates cells with the targeted alteration and selects resistant clones. In our case, the biopsy at second progression revealed *KRAS* G13C, *TP53* R175H, and *EML4::ALK* alterations. This finding suggests that either this clone was present at first progression but not detected, or the fusion remained below the detection threshold while the mutations dominated.

The rapid progression observed under ALK inhibitors in our case could also be partly explained by the pathogenic TP53 variant, a marker of poor prognosis associated with reduced response rates to targeted therapies (28).

Finally, optimal therapeutic strategies for patients harboring concomitant *ALK* and *KRAS* alterations remain undefined. According to the ESMO Clinical Practice Guidelines (4) and recent management updates (5), the treatment of progression on second-generation TKIs such as alectinib is guided by the nature of the resistance mechanism. While third-generation TKIs such as lorlatinib are highly effective against secondary mutations occurring directly within the ALK kinase domain (on-target resistance) (7), they are generally ineffective when resistance arises from the activation of alternative signaling pathways that bypass the ALK inhibition (off-target resistance). In our case, the emergence of *KRAS* variants represents a bypass track that allows the tumor to maintain downstream MAPK/ERK signaling even if the ALK fusion protein is successfully blocked by the TKI.

As highlighted by Toyokawa and Seto (13), the reactivation of downstream signaling through *KRAS* variants bypasses the ALK inhibition, rendering sequential TKI therapy potentially ineffective. In our case, the extensive *KRAS* mosaicism poses a unique challenge for specific targeted therapies. Consequently, for such heterogeneous resistance, platinum-based chemotherapy represents a more robust and reliable option to address the diverse tumor cell populations (4,5). This underscores the

necessity of repeat molecular profiling to distinguish between *ALK*-dependent resistance and complex bypass mechanisms like the mosaicism described here, ensuring that patients are not maintained on ineffective targeted therapies.

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Availability of data and materials

The DNA and RNA sequencing data generated in the present study may be found in the National Center for Biotechnology Information BioProject database under accession number PRJNA1416035 or at the following URL: https://www.ncbi.nlm.nih.gov/bioproject/?term=PRJNA1416035. The other data generated in the present study may be requested from the corresponding author.

Authors' contributions

AS made substantial contributions to the conception of the study, analyzed the data, and wrote the manuscript. GT was involved in the acquisition and interpretation of the clinical data. PG, JLM and AH assisted in the study design and revised the manuscript critically for important intellectual content. AS and AH created the figures. GG and AL performed the pathological analysis and provided the histopathological slides. GP, MH, IH, PG and AH contributed to the genomic analysis and data interpretation. PG, AH and JLM confirm the authenticity of all the raw data. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Written informed consent for both participation and the publication of the patient's individual data, including all text and images, was obtained from the patient. This consent was obtained in accordance with the principles of the Declaration of Helsinki. Following institutional policies for retrospective case reports, the study was deemed not to meet the definition of human subjects research requiring formal review by the Institutional Review Board of the Regional University Hospital Center of Nancy (Nancy, France).

Patient consent for publication

The patient was informed about the use of their biological, imaging and clinical data for research purposes, and written informed consent was obtained.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, artificial intelligence tools (Gemini 3) were used to improve the readability and language of the manuscript, and subsequently, the authors revised and edited the content produced by the artificial intelligence tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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