Lorlatinib-induced remission in refractory acute myeloid leukemia with an anaplastic lymphoma kinase fusion

Anaplastic lymphoma kinase (ALK) is an oncogenic driver frequently identified in anaplastic large cell lymphoma and non-small cell lung cancer (NSCLC).[1] ALK rearrangements drive aberrant ALK autophosphorylation and constitutive activation of oncogenic tyrosine kinase-mediated signaling pathways. ALK-specific tyrosine kinase inhibitors (TKI) mitigate this overactivation and have significant activity in ALK-positive NSCLC, among other solid organ malignancies.[1] Third-generation ALK TKI such as lorlatinib are potent inhibitors of ALK kinase that result in improved progression-free survival in patients with advanced NSCLC compared to other ALK TKI.[2] Emerging data also support the use of next-generation ALK inhibitors (ALKi) in ALK-positive large B-cell lymphoma, where lorlatinib has induced rapid tumor regression with complete suppression of ALK signaling.[3] Furthermore, ALK-positive and/or rearranged histiocytosis has been reported, with objective responses to ALKi observed amongst patients with this myeloid neoplastic disease refractory to standard therapies.[4]

In leukemia, ALK fusions are reported in several cases of AML and other high-grade myeloid malignancies, most commonly arising from inversion or translocation of chromosome 2 leading to *RANBP2*::*ALK* or *SPTBN1*::*ALK*.[5,6] Interestingly, an association of ALK fusion with monosomy 7 (-7) has been observed in pediatric AML, where *RANBP2*::*ALK* or *SPTBN1*::*ALK* was identified in 14.3% (4/28) of patients with -7 compared to none of the 1,064 without -7.[5,7] Oncogenic ALK mutations have also been identified in acute lymphoblastic leukemia.[8]

First-generation ALK TKI are active in leukemia cell lines and primary patient samples with ALK fusion or mutation.[1,5,8] This observation led to the evaluation of crizotinib in AML patients with oncogenic ALK fusions, where remissions have been observed with crizotinib and gilteritinib, a TKI predominantly utilized in *FLT3*-mutated AML which also targets ALK.[9-11] However, results are mixed, with reports of crizotinib resistance.[12] Treatment of ALK fusion-associated AML with a third-generation ALKi has not been reported. Here, we present a patient with chemo-refractory, ALK fusion-associated AML with extensive extramedullary disease who experienced complete remission (CR) after treatment with the third-generation ALK TKI lorlatinib. Institutional Review Board (IRB) evaluation determined that oversight was not required for this single-patient case report. Written Health Insurance Portability and Accountability Act (HIPAA) authorization was obtained from the patient prior to submission.

A 23-year-old man presented with intermittent epigastric pain and was found to have marked gastric wall thickening with nodular omental infiltration. Histopathological results from gastric biopsy demonstrated myeloid sarcoma, and cytogenetic analysis detected deletion of chromosome 16. Archer FusionPlex panel (Integrated DNA Technologies, Coralville, IA, USA) utilizing anchored multiplex PCR identified an *STRN*::*ALK* fusion in the gastric tumor biopsy sample, as well as a *FUS*:*ERG* fusion.[13] *STRN*::*ALK* fusion and KSR2 alterations were also detected via Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT), a hybridization capture-based next-generation sequencing (NGS) clinical assay. PET scan demonstrated fluoro-deoxyglucose (FDG) avid sigmoid colon thickening, hepatic lesions, abdominal lymph nodes, and peritoneal nodules. Bone marrow biopsy (BMBx) demonstrated no morphologic AML; abnormal myeloid blasts were detected at $4x10^{-5}$ cells/total nucleated cells using multiparameter flow cytometry (MFC). Cerebrospinal fluid (CSF) involvement by AML was noted at diagnosis, with abnormal myeloid blast population representing 6.2% of white blood cells (WBC) by MFC. CSF samples were insufficient for analysis for presence of *STRN*::*ALK* fusion.

The patient was initially treated with 7+3 (cytarabine and daunorubicin) without response based on imaging re-assessment. A second induction consisting of FLAG-IDA (fludarabine, cytarabine, G-CSF, and idarubicin) was attempted. Post-therapy PET revealed partial response of intra-abdominal disease. He was then treated with one cycle of high-dose cytarabine-based consolidation with progression of his abdominal lesions. He subsequently received one cycle of azacitidine and venetoclax with no response. Throughout all lines of treatment, intrathecal chemotherapy was administered with alternating cytarabine and methotrexate in addition to systemic therapy; however, central nervous system (CNS) disease persisted.

Given the presence of *STRN*::*ALK* fusion with persistent CNS involvement, the patient was started on lorlatinib 100 mg daily, which has known potent CNS activity.[2] Twelve days after initiation of therapy, PET scan demonstrated near-complete metabolic resolution of all previously FDG-avid extramedullary leukemia (Figure 1A, B). On day 26 of lorlatinib, BMBx revealed no morphologic AML with abnormal myeloid blast population representing 0.008% of WBC by MFC. CNS disease was persistent as of day 29, with abnormal myeloid blast population representing 24.7% of WBC. He was treated with 1,200 cGy of cranio-spinal irradiation (CSI) with complete clearance of his CSF based on MFC analysis. Due to concern for potentiation of CNS toxicity, lorlatinib was suspended after day 49 and memantine was initiated. Lorlatinib was resumed three days after completion of CSI and suspended

again two weeks later, on the day of his admission for allogeneic hematopoietic cell transplantation (alloHCT).

The patient underwent alloHCT using an HLA-matched sibling donor with myeloablative total body irradiation-based conditioning (150 cGy delivered twice daily for a total dose of 1,200 cGy) and graft-*versus*-host disease (GvHD) prophylaxis using tacrolimus, methotrexate and abatacept. His initial post-transplant course was uncomplicated, and lorlatinib was planned to resume on day +60 considering the drug-drug interactions with anti-fungal and anti-viral prophylaxis necessary during the early post-transplant period. However, on day +38 post alloHCT, he developed intermittent non-neutropenic fever, nausea, and appetite loss. Infectious work-up was unrevealing. PET showed new intensely FDG avid circumferential wall thickening of the gastric body, suspicious for recurrent disease. Gastric biopsy confirmed relapsed myeloid sarcoma, weakly positive by ALK immunohistochemistry (IHC) staining. ALK IHC was retrospectively attempted on initial diagnostic gastric biopsy; however, there was insufficient tissue remaining for staining. CSF remained clear of leukemic involvement. Tacrolimus was tapered and lorlatinib was resumed upon relapse diagnosis, with rapid improvement in symptoms. As of day +100, he has not experienced signs or symptoms of GvHD.

Here, we demonstrate that the third-generation ALKi lorlatinib has robust clinical activity in a patient with ALK-rearranged AML. This promising activity warrants further investigation in this unique disease subset. AML with extensive extramedullary involvement refractory to multiple lines of therapy carries an extremely poor prognosis. However, our patient experienced CR of significant abdominal lesions as well as persistent CNS disease after combined modality treatment with lorlatinib and CSI, allowing consolidative alloHCT.

While responses to other ALK TKI such as crizotinib have been reported in the literature, the development of lorlatinib has introduced a more effective molecularly targeted monotherapy which may be considered in patients with ALK fusion-associated AML refractory to standard therapies.[2,9-12] In addition, lorlatinib possesses potent activity against CNS disease in solid tumors, though it can also be associated with cognitive side effects which need to be carefully considered in patients with active CNS involvement, particularly amongst those requiring CSI.[2] In this case, lorlatinib was suspended during CSI to mitigate toxicity risk and memantine was administered for cognitive preservation. Notably, *STRN*::*ALK* fusion analysis could not be performed on the CSF due to specimen limitations, so there is uncertainty about the susceptibility of the CNS disease to lorlatinib. In terms of ultimate CNS disease clearance, the timing of this after CSI favors the hypothesis that radiation was the major driver of clearance.

To our knowledge, the *STRN*::*ALK* fusion identified in this case represents the first report of this particular ALK fusion in AML, distinct from the previously described *RANBP2*::*ALK* and *SPTBN1*::*ALK* fusions (Table 1).[5,6] This rearrangement joins the N-terminal coiled region of STRN exon 3 to the C-terminus of *ALK* exon 20 (Figure 2A-C), preserving the ALK tyrosine kinase domain and likely promoting ligand-independent ALK activation. Also unique in this case was the cytogenetic profile, identifying deletion 16 without -7, an abnormality detected in the majority of ALK fusion-associated AML reported cases.[5,7] With *RANBP2*::*ALK* or *SPTBN1*::*ALK* being identified in 14.3% of pediatric patients with AML with -7 in a pediatric cohort, it may be reasonable to consider evaluation for ALK fusions in patients with AML with -7 refractory to standard therapies to determine candidacy for ALKi, and further work is needed to characterize the frequency of this fusion in adult AML.[5]

An in-frame *FUS* exon 7-*ERG* exon 11 fusion, a recurrent leukemia-associated transcription factor rearrangement linked to adverse outcomes, was also detected and may have contributed to the refractory phenotype.[13] NGS additionally identified a *KSR2* exon 4 missense variant (p.R234H), a kinase suppressor Ras (KSR) family scaffolding protein involved in the activation of MAPK signaling pathways.[14] Although the pathogenic relevance of these co-alterations remains uncertain, these may reflect co-operative pathway modulation, or alternatively, passenger or germline events. Notably, previously reported cases of ALK fusion-associated AML have largely been described on the basis of cytogenetics without NGS data, and the broader molecular landscape of ALK-rearranged AML remains unknown.

Our findings underscore that ALK fusions may occur within a high-risk genomic context, supporting comprehensive genomic profiling, including DNA- and RNA-based sequencing and fusion detection, in extramedullary AML where actionable lesions and kinase pathway alterations may be enriched.[15] NGS may also enable identification of clinically

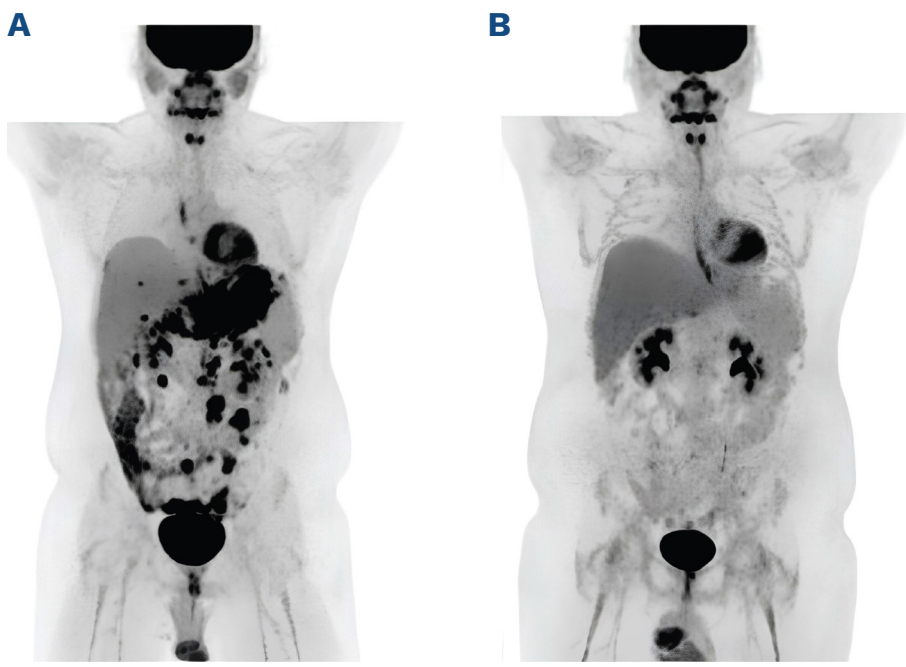


Figure 1. FDG-PET maximum intensity projection images. (A) Pre-lorlatinib and (B) post-lorlatinib (day +12), demonstrating rapid near-complete metabolic resolution of extensive intra-abdominal extramedullary disease.

Table 1. Reported cases of acute myeloid leukemia harboring ALK fusions.

Reference	Age/sex	ALK fusion	Cytogenetics	-7	TKI	Clinical outcome
Rottgers *et al.* (2010)	8 yr/M	RANBP2-ALK	45,XY,inv(2)(p23q13),7/46,XY[5]	Yes	NA	Primary induction failure to ADE, death on day 26 attributed to septic shock
Rottgers *et al.* (2010)	16 yr/M	RANBP2-ALK	45,XY,inv(2)(p23q13),7[8]/46,XY,inv(2)(p23q13)[3]	Yes	NA	Relapsed 6 months after ADE induction → FLAD followed by alloHCT (MSD, conditioned with busulfan, melphalan and thiotepa), alive in CR 6 years post-HCT
Rottgers *et al.* (2010)	3 yr/M	RANBP2-ALK	45,XY,t(2,2)(p23,q11B13),7	Yes	NA	Primary induction failure to ADE → alloHCT (MUD, busulfan, fludarabine and melphalan), alive in CR 8 years post-HCT
Lim et al. (2014)	31 yr/F	RANBP2-ALK	45,XX,inv(2)(p23q21),–7[20]	Yes	NA	Primary induction failure to 7+3 → MEC with CR. Relapsed shortly after → alloHCT (MUD), relapsed 3 months post-HCT, died 7 months after relapse, death attributed to pneumonia
Maesako (2014)/ Takeoka (2015)	75 yr/F	RANBP2-ALK	46,XX,inv(2)(p23q13)[1]/,45,idem,–7[8]/46,idem, –7,+mar[1]	Yes	Crizotinib	Relapsed 3 months after induction with 7+3 → refractory to azacitidine → crizotinib with brief MRD+CR, relapsed 4 months after with heterozygous mutation at the ALK nucleotide position g.716751G>C within exon 25, causing p.G1269A amino acid substitution within the ALK kinase domain
Hayashi *et al.* (2016)	2 yr/F	RANBP2-ALK	45,XX,inv(2)(p23q13)[20]	No	Crizotinib	Relapsed 6 months after induction with MEC → refactory to FLAG-IDA → refractory to azacitidine → crizotinib with MRD-CR, proceeded to haploHCT, alive in CR 1 year post-HCT
Manselle *et al.* (2023)	1 yr/M	RANBP2-ALK	45,X,inv(2)(p13q14),–7[15]/46, XY[5]	Yes	NA	NR
Manselle *et al.* (2023)	1 yr/M	SPTBN1-ALK	45,XY,–7[24]	Yes	NA	NR
Manselle *et al.* (2023)	9 yr/F	SPTBN1-ALK	45, XX, inv(2)(p21q21), –7[20]	Yes	NA	NR
Manselle *et al.* (2023)	1 yr/NR	SPTBN1-ALK	45, XX,–7[20]	Yes	NA	NR
Shekar *et al.* (2023)	18 yr/F	RANBP2-ALK	45,XX,inv(2)(p23q13)[18]	No	Crizotinib	Induction with CPX-351 and GO with MRD+CR → cytarabine, daunorubicin and crizotinib with MRD-CR, followed by alloHCT (MUD, conditioned with alemtuzumab, busulfan, and cyclophosphamide), alive in CR 6 months post-HCT
Adashek *et al.* (2024)	75 yr/F	RANBP2-ALK	45, XX, inv(2)(p23q13), –7[20]	Yes	Gilteritinib	Azacitidine/venetoclax with brief MRD+CR → decitabine, venetoclax, and GO with no response → gilteritinib with MRD-CR, alive in CR 14 months after starting gilteritinib

ADE: arabinoside, daunoblastin, etoposide; ALK: anaplastic lymphoma kinase; alloHCT: allogeneic hematopoietic cell transplantation; CPX-351: liposomal daunorubicin/cytarabine; CR: complete remission; F: female; FLAD: fludarabine, arabinoside, liposomal daunorubicin; FLAG-IDA: fludarabine, arabinoside, granulocyte colony-stimulating factor, idarubicin; G-CSF: granulocyte colony-stimulating factor; GO: gemtuzumab ozogamicin; haploHCT: haploidentical hematopoietic cell transplantation; HCT: hematopoietic cell transplantation; M: male; MEC: mitoxantrone, etoposide, cytarabine; MRD: measurable (minimal) residual disease; MRD+CR: complete remission with detectable MRD; MRD-CR: complete remission with undetectable MRD; MSD: matched sibling donor; MUD: matched unrelated donor; NA: not applicable; NR: not reported; TKI: tyrosine kinase inhibitor; yr: years.

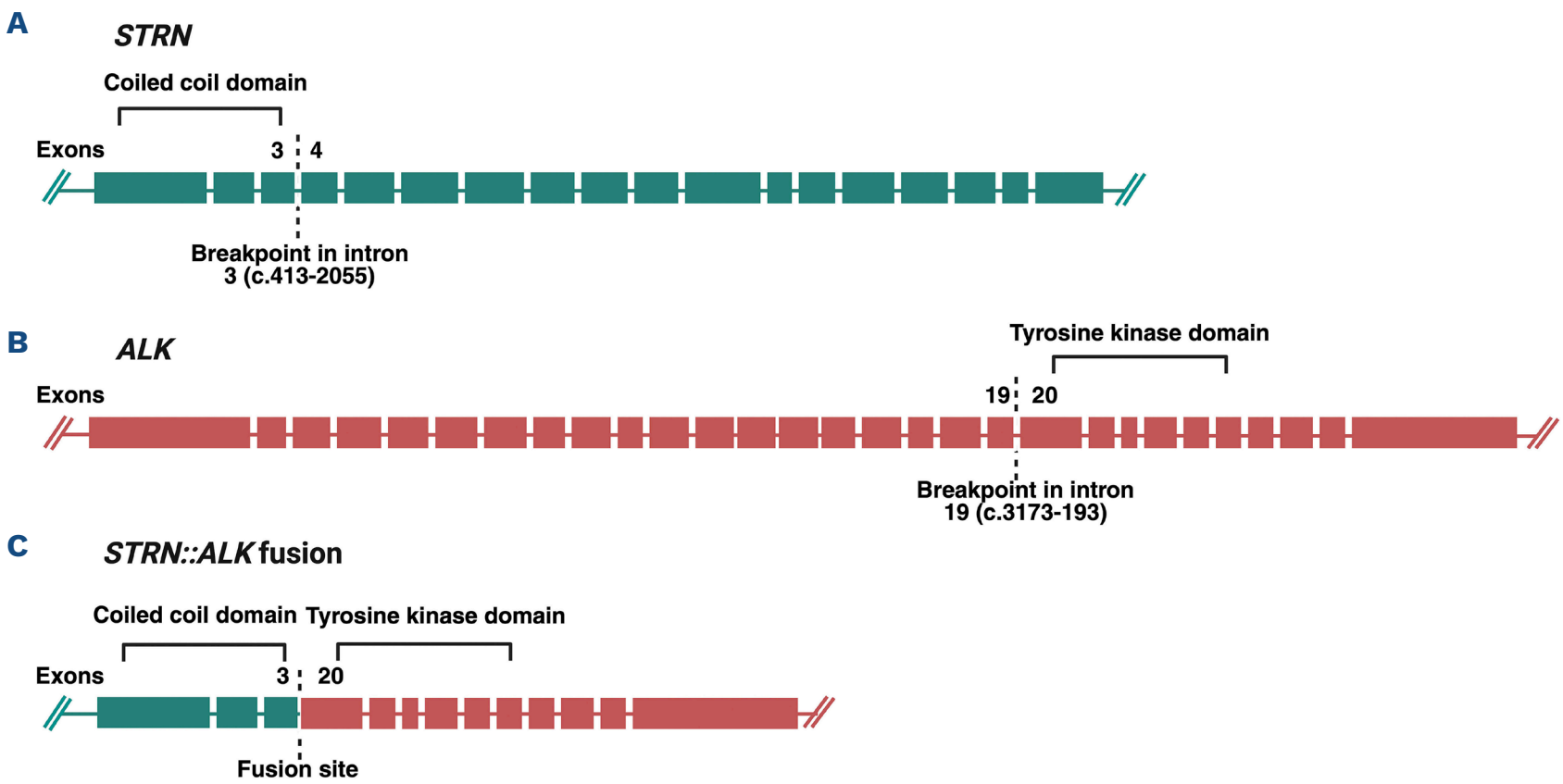


Figure 2. Genomic structure and predicted in-frame *STRN*::*ALK* fusion identified by next-generation sequencing. (A) Schematic of *STRN* (NM_003162) exon structure, highlighting the coiled coil domain and the reported breakpoint in intron 3 (*c.413-2055*), occurring between exons 3 and 4. (B) Schematic of *ALK* (NM_004304) exon structure, highlighting the tyrosine kinase domain and the reported breakpoint in intron 19 (*c.3173-193*) occurring between exons 19 and 20. (C) Predicted *STRN*::*ALK* fusion transcript, resulting in retention of the STRN coiled coil domain and the ALK tyrosine kinase domain, consistent with a constitutively active ALK fusion.

relevant co-alterations beyond the *ALK* rearrangement itself. With the rapid advancement in approvals for molecularly targeted drugs progressing across malignancies, consideration should be given to the utility of disease-agnostic therapeutics in promoting cancer cell death, particularly in refractory AML with unique genetic signatures generally observed in solid malignancies.

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Contributions

LB and NTO conceptualized the study, collected data, performed the chart and literature review, and wrote the manuscript. BS and EMS conceptualized the study and wrote the manuscript. MDE collected data and wrote the manuscript. BSI and MG wrote the manuscript. All authors reviewed and approved the final version of the manuscript for publication.

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Data-sharing statement

The data supporting this report are available from the corresponding author upon request, subject to approval to ensure patient privacy.

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