Case Report

Identification and Development of a Lung Adenocarcinoma PDX Model With *STRN-ALK* Fusion

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Clinical Practice Points

- Gene fusions involving the anaplastic lymphoma kinase gene (*ALK*) often leads to oncogenic activation of the *ALK* kinase resulting in tumor development in lung and other solid tumors. Accurate identification of the fusion gene in patients with lung cancer has profoundly impacted patients' clinical performance and long-term survival.
- In this report, we describe the discovery and the generation of a patient-derived tumor (PDX) model in mice for a lung adenocarcinoma with the rare *STRN-ALK* gene fusion. Using tissues from this PDX, we were able to perform extensive genomic analyses to fully characterize the molecular rearrangements resulted in this fusion gene. At more than 6 years post initial diagnosis, the patient continues to respond to tyrosine kinase inhibitor treatment despite systematic disease demonstrating the tumor is still sensitive to targeted therapy.
- In depth evaluation of the available reports on tumors with this same fusion suggested that 5′ partner of the oncogenic *ALK* fusion may play a critical role affecting the long-term response to tyrosine kinase inhibitor therapy observed in this and other reported patients with the same fusion.
- Our clinical experience using PDX models to guide clinical treatment in advanced stage lung cancer are also discussed to help inform the design of similar clinical studies in the future.

Clinical Lung Cancer, Vol. 20, No. 2, e142-7
Keywords: 5′ Fusion partner, Gene fusion, SCID-Beige mice, Survival, Targeted therapy

Introduction

In a subset of lung adenocarcinomas, gene fusions involving the anaplastic lymphoma kinase gene (*ALK*) transcript act as the primary driver of tumorigenesis.[1] Several small molecule compounds, such as crizotinib, ceritinib, alectinib, and brigatinib, can effectively inhibit *ALK* activation in lung cancer, resulting in significant disease control.[2] However, these drugs are not curative, and patients eventually develop resistance in most cases sometimes after the start of the treatment.[3]

Fusions involving *STRN-ALK* genes were first identified in lung cancer through a kinome capture approach, but only 3 cases with this fusion have been reported in lung cancer to date.[4-6] Here, we

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Submitted: Aug 31, 2018; Revised: Oct 29, 2018; Accepted: Nov 12, 2018; Epub: Nov 20, 2018

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1525-7304/$ - see frontmatter
https://doi.org/10.1016/j.cllc.2018.11.002

describe the establishment and molecular characterization of patient-derived xenograft (PDX) from a patient who presented with a stage IV lung adenocarcinoma carrying the *STRN-ALK* fusion and exceptional survival.

Materials and Methods

PDX Development

An 18-gauge needle was used under computed tomography (CT) guidance, and tissues from 4 cores were collected and split as 2 each for routine pathology and PDX development under Institutional Review Board-approved protocol. For PDX growth, female 6 to 8 weeks old SCID-Beige mice (C.B.-17) were used, and 1 core was injected subcutaneously on the flank, whereas the other was implanted onto the fat pad around the kidney under Institutional Animal Care and Use Committee-approved protocol. All methods were performed in accordance with the Mayo Clinic guidelines and regulations. The subcutaneous tumor growth was monitored regularly by palpation, and the tumor around the renal fat pad was scanned by ultrasound (National Ultrasound, Duluth, GA). Tumors became palpable at about 6 months and were harvested at 268 days after the initial implant. After the initial harvest, tumors were passaged on to a subsequent generation of mice when the tumor-bearing mice were moribund. For long-term storage, aliquots of PDX tumor fragments were slow frozen to −80°C and then transferred to storage in liquid nitrogen.

Immunohistochemistry (IHC) for ALK

Four-micron sections cut from formalin-fixed paraffin-embedded blocks were placed on charged slides; the slides were then dried and melted in a 62°C oven for 20 minutes. IHC staining was performed as follows: slides were placed on a Ventana BenchMark XT slide staining system (Ventana Medical Systems Inc, Tucson, AZ) for staining. The staining protocol included on-line deparaffinization, heat-induced epitope retrieval with Ventana Cell Conditioning 1 for 32 minutes, and primary ALK antibody (Cell Signaling Technology, Danvers, MA) incubation for 32 minutes at 37°C (clone D5F3, a rabbit monoclonal antibody, in a 1:100 dilution). Antigen-antibody reactions were visualized using the Ventana Optiview Universal DAB Detection Kit. Counterstaining was performed on the Ventana BenchMark XT using Ventana hematoxylin II for 8 minutes followed by bluing reagent for 4 minutes. The positive control was a known ALK-rearranged lung adenocarcinoma, and the negative control was a mouse immunoglobulin G1 serum substitution for the primary ALK antibody. Histopathologic characterization and IHC scoring of all tissue sections were conducted independently by 2 practicing pulmonary pathologists (JEY and HZR).

Fluorescent in Situ Hybridization (FISH)

Commercially available ALK Break-apart probe (Abbott Molecular/Vysis Products) consisting of 3′ ALK DNA labeled with SpectrumOrange and 5′ ALK DNA labeled with SpectrumGreen were combined as 1 probe set. The dual color, break-apart rearrangement probe was applied to individual slides, hybridized, and washed according to the partially automated tissue FISH protocol. ALK gene rearrangement was considered by the separation of the 2 probes and/or a loss for 1 of the probes.

Next Generation Sequencing and Bioinformatics Analyses

Genomic DNA and total RNA were extracted from snap frozen PDX tumors using the Allprep Kit from Qiagen. TruSeq mRNA V2 kit was used to generate RNAseq libraries and sequenced as paired ends and 101 cycles. Mate pair sequencing (MPseq) analysis was done by mapping to GRCh38 with BIMA,[7] and structural variant calls were reported with SVAtools.[8,9] Both libraries were sequenced at 3 samples/lane on HiSeq 2500. RNAseq were analyzed using MapRseq protocol.[10]

For RNAseq, 90% reads mapped to the genome and over 80% reads mapped to annotated genes. To assess mutation signature, we filtered for variants with read depth $>$ 30, having genotype quality $\geq$ 30, without an rsID, and removed artifact variants that are located at ends of the reads to arrive at 520 variants. We then examined the fraction of mutation signatures in the PDX in each category and the following is the order of signatures obtained:

Signature	No. of Variants
C>T	199
T>C	147
C>G	71
C>A*	45
T>G	35
T>A	23

Results

Case Summary

The patient was a 52-year-old Caucasian, never-smoking female, with a history of second-hand smoking exposure as a child from both parents. She presented with increasing dyspnea and was found to have a malignant pleural effusion. At the time of the initial diagnosis, a lower right lung 1.3−cm-sized nodule was biopsied and found to be a lung adenocarcinoma positive for an *ALK* gene rearrangement (Figure 1A). The patient was treated with crizotinib, which resulted in a durable response for 4 years until evidence of disease progression with an anterior left chest metastasis (Figure 1B) and intracerebral metastases. The patient was then switched to ceritinib in conjunction with whole brain radiation. As of last follow-up, the patient remained stable on ceritinib at 26 months with minimal side effects (Figure l C).

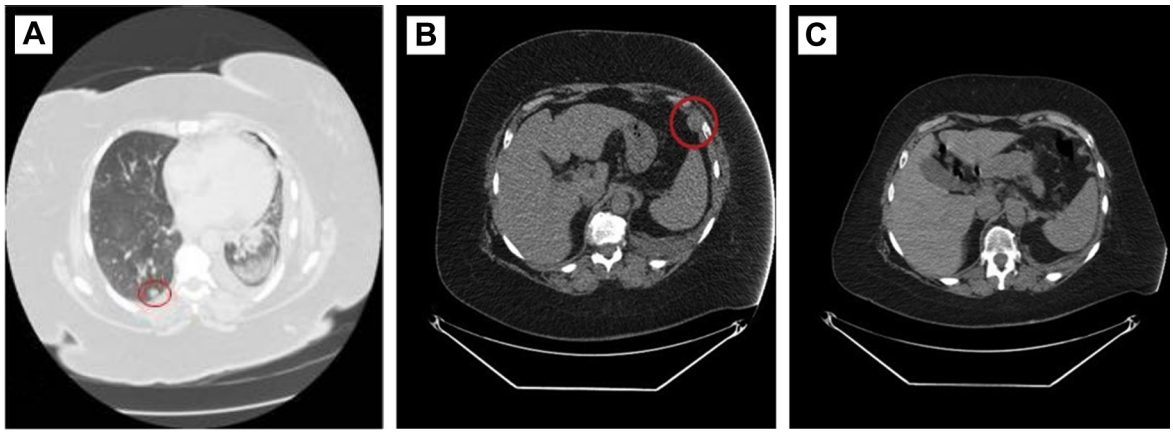
Development of PDX Using CT-guided Biopsies

At the time of tumor progression, the patient was invited and enrolled to participate in a study seeking to develop patient-derived tumor models using tumor biopsies obtained with CT guidance under institutionally approved Mayo Clinic Institutional Review Board and Institutional Animal Care and Use Committee protocols. The biopsies were taken from a chest wall metastasis at the time of progression under CT guidance (Figure 1B). For PDX development, tissue fragments were implanted into SCID-Beige mice either subcutaneously on the flank or the fat pad around the kidney. Tumors at both implanting sites became noticeable at a similar time point and were harvested 267 days after initial implant (Figure 2A and 2B).

Pathology Features of the Tumor Biopsy and PDXs Developed from the Flank and Fat Pad of the Kidney

Pathologic examination of the chest wall biopsy showed mucinous adenocarcinoma with visible signet ring cell features

Figure 1 Images of Chest Computed Tomography Scans of the Patient During *ALK* Inhibitor Treatment. A, One 1.3-cm Adenocarcinoma Nodule was Found in the Right Lower Lung at Initial Diagnosis. B, Chest Wall Metastasized to Anterior Left Eighth rib at the Time of Progression. C, The Patient had an Ongoing Response to Ceritinib at the Time of the Last Follow-up. The Red Circles Indicate the Site of Original Tumor at Diagnosis in (A) and the Site of the Computed Tomography-guided Biopsy in (B)



under H&E staining and strong diffuse ALK positivity (3+) by IHC (Figure 3A and 3B). FISH of the tumor biopsy revealed a chromosome rearrangement involving the *ALK* gene region with loss of the 5` probe (Figure 3C). Hematoxylin and eosin staining showed similar signet-ring cell features and mucous adenocarcinoma appearance, as well as strong ALK positivity by IHC in the subcutaneous flank tumor in a pattern that closely resembled the chest wall biopsy (Figure 3D and 3E). The basic histopathologic findings of the PDX tumor harvested from the fat pad of the kidney (Figure 3F) appeared very similar to that of the subcutaneous tumor, characterized by abundant cytoplasmic mucin with eccentric nuclei resulting in signet ring cell carcinoma features.

Molecular Characterization of the STRN-ALK Fusion

We performed whole transcriptome sequencing using TruSeq mRNA and MPseq of the PDX tumor harvest from the flank to identify gene fusion and genomic rearrangements, respectively.[11] An in-frame fusion between *STRN* and *ALK* genes was identified by RNAseq involving the first 3 exons of *STRN* and exon 20 to 3`end of *ALK* (Figure 4A). The fusion gene appeared to be highly expressed beginning at the exon 20 and extending to 3' end of the *ALK* gene (Figure 4B). However, no resistant mutations of the *ALK* kinase domain were observed. A schematic diagram of the fusion and the predicted fusion protein product is shown in Figure 4C. At the DNA level, MPseq revealed that the fusion was the result of a

Figure 2 First-generation Patient-derived Lung Xenografts in SCID Mice. Solid Tumors Were Found Subcutaneously and Also Around the Fat Pad (Arrows). The Intraperitoneal Tumor was Attached to the Abdominal Wall and Surrounded With Thick Mucus (0.5 mL)

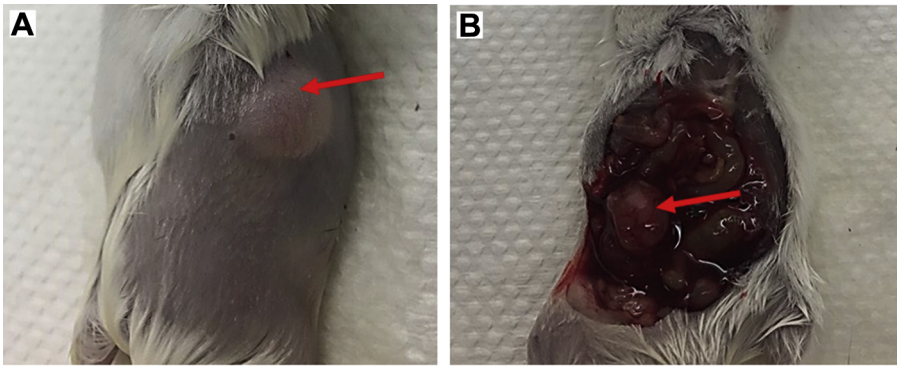
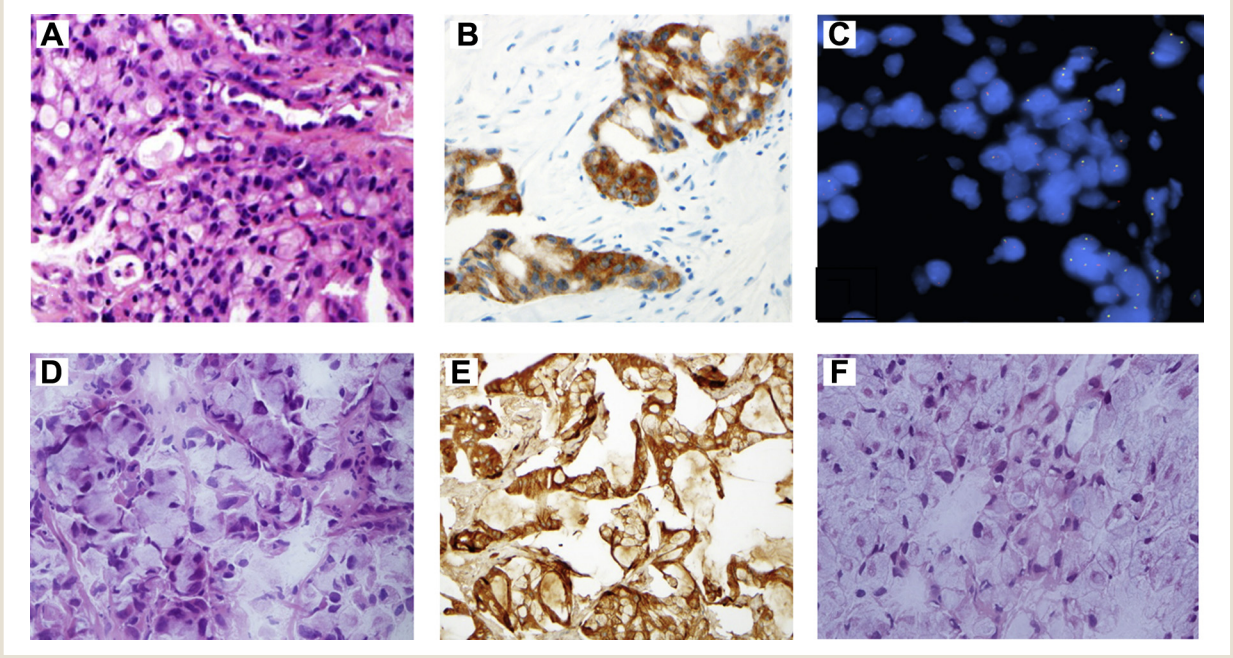


Figure 3 Histopathologic and Fluorescence in Situ Hybridization (FISH) Findings Of the Biopsy and Patient-derived Lung Xenograft (PDX) Tumors Derived From patient's Chest Wall Metastasis. A-C, Hematoxylin and Eosin (H&E) (A), ALK Immunohistochemical Stain (Score 3+) (B) and FISH Analyses (C) of the Tumor Biopsy Obtained From the Metastasis to the Chest Wall. ALK Break-apart FISH Probe Indicates Rearrangement of *ALK* With Loss of the 5`*ALK* (gr) Signal (C). D, E, H&E (D) and Immunohistochemical (E) Stains for the PDX From the Subcutaneous Tumor Implanted in the Flank. F, H&E of the PDX Grown on the Fat Pad of the Kidney



deletion between 29.2 MB to 36.9 MB (~7.7 MB) regions on chromosome 2p involving *STRN* and *ALK* genes (Figure 4D and 4E). In addition, the tumor is tetraploid for several chromosomes with a complete loss of the *CDKN2A* gene on chromosome 9p (Figure 4E).

Mutational Signature of the PDX

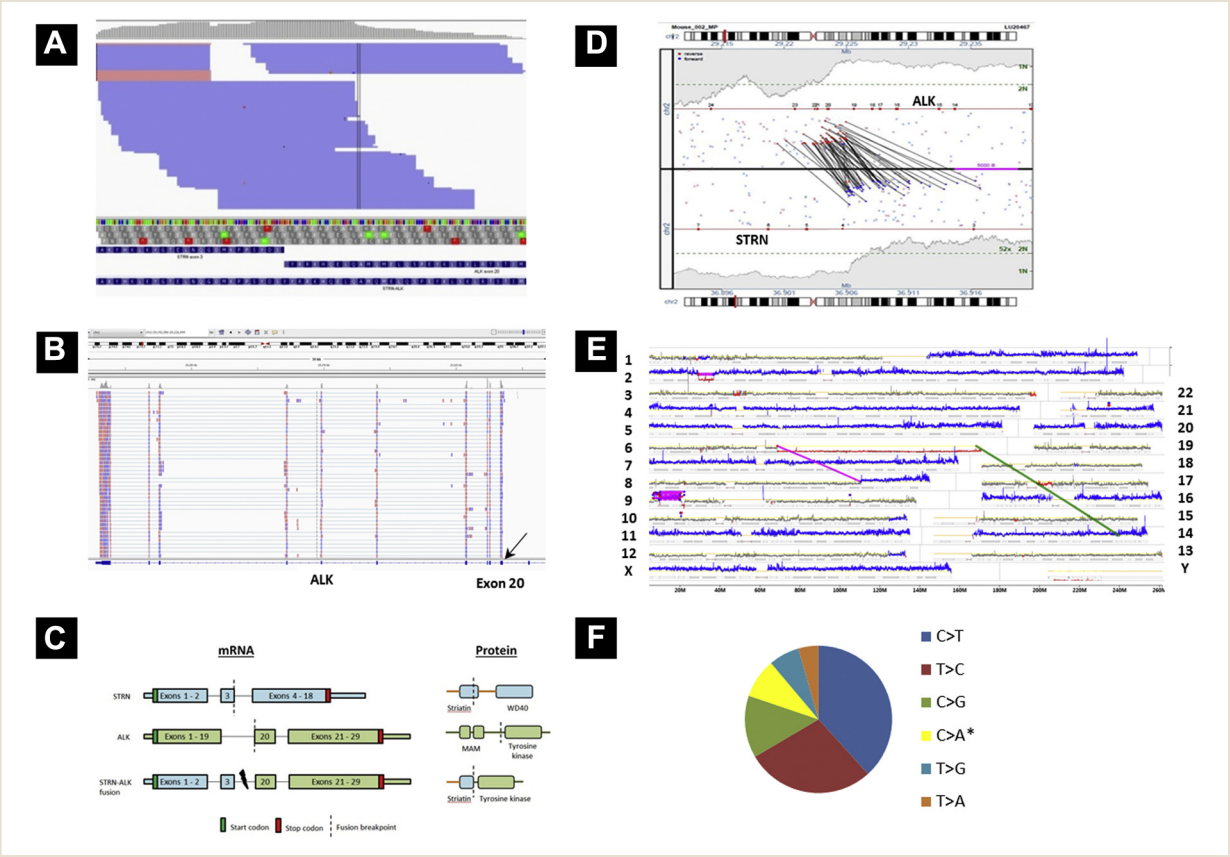
We performed mutational signature[12] analysis using stringent criteria to identify single nucleotide variants obtained by RNAseq and to assess the molecular etiology of the tumor with *STRN-ALK* fusion. Although having a strong history of second-hand smoking exposure, smoking associated C>A mutational pattern (Signature 4) was not a dominant pattern in this tumor (Figure 4F). In contrast, the C>T (Signature 1, spontaneous deamination of 5-methylcytosine) was the most prominent feature followed by T>C (Signature 12, which exhibits transcriptional strand bias with unknown etiology).

Discussion

Gene fusion in lung cancer is important clinically because it is often the primary driver of oncogenesis and renders the host tumor highly sensitive to targeted therapy. Since initial identification of *EML4-ALK* fusion in non–small-cell lung cancer (NSCLC),[1] several fusion partners to the *ALK* gene (*KIF5B, KLC1, TFG, TPR, HIP1, STRN, DCTN1,* and *SQSTM1*) have been identified.[13] In most studies, the clinical outcome associated with these fusion partners are not well-described except those with the *EML4-ALK* fusion, which appear to have a less favorable survival outcome compared with other NSCLC cases in the absence of targeted therapy.[14] Tyrosine kinase inhibitors, such as crizotinib and ceritinib, which specifically inhibit the activating ALK, have demonstrated significant clinical benefits in patients with lung carcinomas and mesenchymal tumors harboring the *ALK* fusion.[15,16] For patients with the *EML4-ALK* fusion variants, the overall treatment responses are similar, with a mean disease-free survival time between 10 and 20 months while still on crizotinib.[15,17] When stably expressed in NIH3T3 cells, ALK fused with 7 different 5′ partners exhibited a 5- to 10-fold difference in sensitivity to targeted drugs.[18]

Although relatively rare in occurrence, *STRN-ALK* fusion has been detected in several different cancer types including NSCLC,[4-6] renal cell carcinomas,[19] colorectal and papillary thyroid cancers[20-22] (Table 1). Functionally, gene fusion involving *STRN* results in constitutive activation of *ALK* kinase via dimerization mediated by the coiled-coil domain of the 5′ gene.[21] Nakanishi et al[6] reported a patient with *STRN-ALK*–fusion-positive NSCLC that was resistant to alectinib treatment and who died 6 months after the initial diagnosis without a detectable *ALK* resistance mutation in the tumor. In contrast, the patient described in this report had stable disease for 4 years while on crizotinib and continues to exhibit stable disease more than 2 years after switching to ceritinib. A similar favorable response was also reported in another NSCLC case with a *STRN-ALK* fusion in a nonsmoker male patient identified through

Figure 4 **Identification of *STRN-ALK* Fusion in the Patient-derived Lung Xenograft (PDX) Mouse Tumor by Next Generation Sequencing. A, Rearrangement of *STRN* and *ALK* Genes as Detected by RNAseq. B, High Expression of ALK Transcript from Exon 20 to 3′ of the gene. C, Schematic Representation of the *STRN-ALK* Fusion. D, SVAtools' Junction Plot Illustrating the Position of Uniquely Mapped Mate-pair Reads From the Intronic Regions of *STRN* (Intron 3) to *ALK* (Intron 20) on Chromosome 2. Vertical and Oblique Black Lines Represent Aberrant Read-pairs; Blue Ends Indicate Mapping to Positive DNA Strand, Whereas Red Ends Indicate Mapping to the Reverse DNA Strand. Shaded Gray Areas Show the Copy Number Relative to the Bridged Coverage of the Sample at 52x. E, Genome Plot of Copy Number Changes and Chromosomal Rearrangements for Each Chromosome. Pink Areas Indicate the Significant Deletions on Chromosome 2 and Chromosome 9. F, Relative Fraction of Mutation Signatures in the PDX**



circulating tumor DNA analysis in the plasma.[5] In the 2 reported renal cell carcinoma cases with *STRN-ALK* fusion, 1 of the 2 patients had an exceptional survival at > 20 years after surgery alone, likely the result of being at an early stage at the time of diagnosis, but this may also reflect the biological nature of the cancer.[19] Finally, remarkable responses to crizotinib treatment were also reported for patients with colorectal and thyroid carcinoma having *STRN-ALK*-positive tumors (Table 1).[21,22]

Consistent with clinical features commonly associated with *ALK*–fusion-positive lung cancers, the patient with the *STRN-ALK* fusion that we identified in this study is a female never-smoker. Although having a history of childhood second-hand exposure to smoking by both parents, the mutational signature and pattern of chromosomal alterations observed in this tumor jointly points to the activation of *ALK* upon its fusion to the *STRN* gene as the most likely oncogenic driver contributing to the onset of lung cancer in this case.[12]

Finally, our experience developing PDX models using CT-guided biopsies from clinically advanced lung cancer highlights some of the critical factors that contributed to the success and challenges with this approach, particularly for patients with fusions involving the *ALK* gene fusions: (1) Although one of the most targetable genetic alterations, fusions involving *ALK* remain rare, accounting for only a small fraction of NSCLC even in enriched populations.[14] (2) Most patients with *ELM4-ALK* gene fusions experience disease progression while on tyrosine kinase inhibitors within 10 to 20 months on average.[15,17] In contrast, the patient in our study had a *STRN-ALK* gene–fusion-positive tumor and remained sensitive to the targeted therapy with exceptionally long survival (> 72 months). Furthermore, 4 of the 7 reported patients having the same fusions were still alive for 24 months or longer at the time of the report.[5,19,21] Together with functional studies in NIH3T3 cells overexpressing the fusion genes,[18] this evidence jointly supports the hypothesis that 5′ partner of the *ALK* gene fusion can affect the duration of the clinical response to tyrosine kinase inhibitor treatment in ALK–fusion-positive tumors. (3) In our experience generating PDX models, the site of initial implant did not appear to affect the tumor growth as they became

Table 1 *STRN-ALK* Fusions and Survival Status in Cancer

Cancer Type	No. Cases	OS, mos	PFS, mos	Vital Status	References
NSCLC	1	NA	NA	NA	4
	1	6	3	Dead	6
	1	36	29	Alive	5
RCC	2	3	3	Alive	19
		324	168	Alive	
PTC	1	24	6	Alive	20
	1	6	NA	Dead	21
Colon cancer	1	39	18	Alive	22

Abbreviations: NA = not available; NSCLC = non–small-cell lung cancer; OS = overall survival; PFS = progression-free survival; PTC = papillary thyroid cancer; RCC = renal cell carcinoma.

palpable at about the same time either embedded subcutaneously or in the renal capsule in littermate animals. Pathologic examinations showed that both PDXs exhibited indistinguishable morphologic features that were characteristic of signet ring cells commonly associated with ALK-positive lung cancers. However, only 1 of the 14 implanted tumors successfully generated a viable tumorgraft under protocol using CT-guided needle biopsy approach. This low take-rate is in sharp contrast to our 74% take-rate using surgically resected ovarian cancers.[23] Although many other factors such as tumor type, tumor grade, pretreatment status, tumor fraction in the sample, and size of the tumor tissue could affect the overall success rate, this result suggests that PDX models might be more suited using surgically resected primary tumors where large untreated tissue samples are likely available for implantation.[24] Finally, the extended lag time (8 months in this study) for PDX models to establish from small needle biopsies also likely limits its use for effective treatment monitoring and drug selection in most clinical settings, particularly in late-stage cancers. Nevertheless, the successful generation of a PDX lung adenocarcinoma model carrying the rare *STRN-ALK* fusion provided a renewable resource for us to comprehensively examine the detailed molecular changes in the patient's tumor after its progression on crizotinib treatment and enables future studies to examine the biological mechanism underlying the long-term response of *STRN-ALK* fusion to targeted therapy drugs.

Acknowledgments

This study was supported by the National Foundation for Cancer Research Hillsberg Lung Cancer Translational Research Grant, Mayo Clinic Cancer Center, and the Center for Individualized Medicine. The authors thank Darlene Knutson and Sara Kloft-Nelson from the Mayo Cytogenetics Core for performing the FISH analysis; Drs John Weroha, Dennis Wigle, and George Vasmatzis for their support during the course of this study; and Dr Angela Davies from the Champion Oncology for helpful discussions.

Disclosure

The authors have stated that they have no conflicts of interest.

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