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Cancer Diagnostics and Molecular Pathology

ALK Fusions in a Wide Variety of Tumor Types Respond to Anti-ALK Targeted Therapy

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. ALK • Fusion • Crizotinib • Alectinib • Comprehensive genomic profiling • Rearrangement

Abstract

Background. Genomic fusions of the anaplastic lymphoma kinase gene (*ALK*) are a well-established therapy target in non-small cell lung cancer (NSCLC). From a survey of 114,200 clinical cases, we determined the prevalence of *ALK* rearrangements (r*ALK*) in non-NSCLC tumors and report their responsiveness to therapies targeting ALK.

Materials and Methods. Comprehensive genomic profiling of 114,200 relapsed and metastatic malignancies, including both solid tumors and hematolymphoid cancers, was performed using a hybrid-capture, adaptor ligation-based next-generation sequencing assay.

Results. Of 114,200 clinical samples, 21,522 (18.8%) were NSCLC and 92,678 (81.2%) were other tumor types. Of the 876 (0.8%) cases with *ALK* fusions (f*ALK*) or rALK, 675 (77.1%) were NSCLC and 201 (22.9%) were other tumor types. *ALK* fusions were significantly more frequent in NSCLC (3.1%) than non-NSCLC (0.2%; $p < .0001$). Patients with non-NSCLC tumors harboring f*ALK* were significantly younger ($p < .0001$) and more often female ($p < .0001$) than patients with f*ALK*-positive NSCLC. *EML4* was more often the fusion partner in NSCLC (83.5%) versus non-NSCLC tumors (30.9%; $p < .0001$).

Conclusion. *ALK* rearrangements can be identified in a wide variety of epithelial and mesenchymal malignancies beyond NSCLC. Anti-ALK therapies can be effective in non-NSCLC tumors driven by f*ALK*, and further study of therapies targeting *ALK* in clinical trials involving a wider variety of cancer types appears warranted. ***The Oncologist*** 2017;22:1444–1450

Implications for Practice: Rearrangements involving the *ALK* gene have been detected in dozens of cancer types using next-generation sequencing. Patients whose tumors harbor *ALK* rearrangements or fusions respond to treatment with crizotinib and alectinib, including tumors not normally associated with *ALK* mutations, such as non-Langerhans cell histiocytosis or renal cell carcinoma. Comprehensive genomic profiling using next-generation sequencing can detect targetable *ALK* fusions irrespective of tumor type or fusions partner.

Introduction

The anaplastic lymphoma kinase gene (*ALK*) encodes a tyrosine kinase receptor with a major role in neuronal development [1–5]. The ALK protein, also known as CD246, was originally identified in anaplastic large cell malignant lymphoma (ALCL) and shown to be overexpressed as a result of a t(2;5)(p23;q35) chromosomal translocation [1]. The original *ALK* fusion partner found in ALCL was *NPM1*, a nucleophosmin, and this fusion is present in 70%–80% of *ALK*-rearranged ALCL [1–5]. A wide variety of additional fusion partners for *ALK* have subsequently been described in ALCL, including *EML4* in <10% of cases [1–5]. The vast majority of *ALK* fusions (f*ALK*) retain the kinase domain and are associated with ALK-driven tumorigenesis, progression, and metastasis [1–5]. The first studies investigating f*ALK* as therapy targets in non-small cell lung cancer (NSCLC) found *EML4* as the sole fusion partner, although a variety of less-common fusion partners have subsequently been identified [6–10]. Over the past 10 years, therapeutic strategies for *ALK*-driven NSCLC have evolved. There are now accepted first-line treatments targeting *ALK*, as well as second- and third-generation inhibitors employed to overcome resistance to prior lines of anti-ALK therapy [6–10]. Standard of care treatment for NSCLC now includes ALK testing when the disease presents in an advanced stage or has progressed after surgical treatment [11].

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The impressive efficacy of targeting f*ALK* in NSCLC and ALCL raised interest in *ALK* alterations in other cancer types. Several studies have shown the efficacy of anti-ALK therapies in a wide variety of malignancies [12–28], but these studies are small-scale and generally limited to individual case reports or case studies. In addition, many of these publications targeted *ALK* alterations that were not classic gene fusions, and included both *ALK* gene amplifications and *ALK*-activating base substitutions [24, 25, 29]. The following study evaluated a series of 114,200 consecutive clinical cases with comprehensive genomic profiles available to identify fALK that could facilitate the use of precision medicine in both NSCLC and non-NSCLC malignancies.

Materials and Methods

A series of 114,200 consecutive clinical cases, across a wide variety of disease types, was analyzed using comprehensive genomic profiling (CGP) in a Clinical Laboratory Improvement Amendments-certified, College of American Pathologists-accredited laboratory (Foundation Medicine, Cambridge, MA), as previously described [30, 31]. Approval for this study, including a waiver of informed consent and a Health Insurance Portability and Accountability Act of 1996 waiver of authorization, was obtained from the Western Institutional Review Board (Protocol 20152817).

The pathologic diagnosis of each case was confirmed on routine hematoxylin and eosin stained slides and all samples forwarded for DNA extraction contained a minimum of 20% tumor nuclear area. In brief, $\geq$50 ng DNA was extracted from 40 microns of tumor sample in formalin-fixed, paraffin-embedded tissue blocks. The samples were assayed by CGP using adaptor-ligation and hybrid capture targeting all coding exons in one of three assay versions: 287 (version 1, FoundationOne [Foundation Medicine, Cambridge, MA, https://www.foundationmedicine.com]), 315 (version 2, FoundationOne) or 405 (version 3, FoundationOne Heme) cancer-related genes plus select introns from 19 (version 1), 28 (version 2), or 31 (version 3) genes frequently rearranged in cancer. A subset of cases was also evaluated by RNA sequencing using $\sim$3M on-target unique pairs for 265 genes. Sequencing of captured libraries was performed using Illumina HiSeq (Illumina, San Diego, CA, https://www.illumina.com) technology to a mean exon coverage depth of $>600\times$, and the resultant sequences were analyzed for base substitutions, insertions, deletions, copy number alterations (focal amplifications and homozygous deletions), rearrangements, and select gene fusions.

All three versions of the CGP assay used in this study detect *ALK* rearrangements (r*ALK*) through DNA sequencing [30, 31]. In addition, version 3 of the assay can detect f*ALK* through RNA sequencing. For the purposes of this study, f*ALK* are defined as genomic rearrangements detected by RNA or DNA sequencing that result in a portion of the *ALK* gene containing the kinase domain (exons 20–29, NM_004304) being fused in-strand to the promoter-containing region of a second gene (at a minimum the 5′ UTR). Fusions detected by RNA were included if they were in-frame. Fusions detected by DNA were included if an in-frame product could be generated during mRNA processing, including by exon skipping. *ALK* rearrangements were defined as any other genomic rearrangement event predicted to separate the exons encoding the ALK kinase domain (exons 20–29, NM_004304) from the upstream exons encoding the regulatory regions.

Tumor mutational burden (TMB) was determined on 0.83 megabase (Mb; version 1), 1.14 Mb (version 2), or 1.23 Mb (version 3) of sequenced DNA using a mutation burden estimation algorithm that, based on the genomic alterations detected, extrapolates to the exome or the genome as a whole (supplemental online Tables 1–3). For purposes of mutation burden estimation, all coding short variant alterations (base substitutions and indels), including synonymous alterations, are counted. Subtracted from this number are functionally oncogenic or germline alterations, as defined below. Germline alterations are those listed in the dbSNP database (http://www.ncbi.nlm.nih.gov/SNP), those with two or more counts in the ExAC database (http://exac.broadinstitute.org), or those predicted by a somatic-germline zygosity algorithm to be germline in the specimen being assessed [32]. Functionally oncogenic mutations are those occurring as known somatic alterations in the COSMIC database (http://cancer.sanger.ac.uk/cosmic) or with likely functional status (disruptive alterations in tumor suppressor genes). Finally, to calculate the mutation burden per Mb, the total number of relevant mutations is divided by the coding region target territory of the test (0.83 Mb, 1.14 Mb, or 1.23 Mb). Tumor mutational burden is categorized as low ($<$6 mutation [mut]/Mb), intermediate (6–20 mut/Mb), or high ($\geq$20 mut/Mb) [32, 33].

Results

Of the 114,200 clinical samples evaluated with CGP in this study, 21,522 (18.8%) were NSCLC and 92,678 (81.2%) were other tumor types (Table 1). The gender and age characteristics of these cohorts are shown in Table 1. Patients with non-NSCLC tumors were significantly younger ($p < .0001$) and more often female ($p < .0001$) than the NSCLC *ALK*-fusion positive patients. *ALK* genomic alterations were found in 1,313 (1.1%) cases, of which 896 (0.8%) harbored r*ALK* (10.9%) or f*ALK* (89.1%) with *EML4* or another partner (Table 2). The *ALK*-altered cases that lacked gene fusions included *ALK* amplifications and a wide variety of short variants, including base substitutions and short insertions and deletions. Of the 876 (0.8%) cases with f*ALK* or r*ALK*, 675 (77.1%) were NSCLC and 201 (22.9%) were other tumor types, and f*ALK* were significantly more frequent in NSCLC (3.1%) than non-NSCLC (0.2%; $p < .0001$). Patients with non-NSCLC tumors harboring f*ALK* were significantly older ($p < .0001$) and more often female ($p < .0001$) than patients with f*ALK*-positive NSCLC. The distribution of tumor histologies is shown in supplemental online Tables 4 and 5. Outside of NSCLC, r*ALK* were most often found in carcinomas (67), sarcomas (39), and hematolymphoid malignancies (24).

EML4 was by far the most common fusion partner in NSCLC (568; 83.5%), with a significant difference versus non-NSCLC tumors (63; 30.9%; $p < .0001$; Table 2). A wide variety of other fusion partners were identified in non-NSCLC tumors, the most frequent being *STRN* and *NPM1* (16 cases each), *TNS1* and *CLTC* (9 cases each), and *ACTG2* (5 cases; Table 2).

The genes most frequently coaltered with f*ALK* in these cohorts are shown in Figure 1. By far the most common were loss of *CDKN2A* and/or *CDKN2B* and inactivation of *TP53*. Less than 1% of *ALK*-rearranged NSCLC featured high TMB ($\geq$20 mut/Mb), compared with 3.5% of non-NSCLC samples with

Table 1. Clinical and genomic features of *ALK* fusion-positive and *ALK* fusion-negative NSCLC and non-NSCLC cases

Parameter	NSCLC	Non-NSCLC	Total
Total cases sequenced, n (%)	21,522 (18.8%)	92,678 (81.2%)	114,200
Gender, female/male	52.6%/47.4%	59.2%/40.8%	
Age			
Mean	55.4	43.0	
Median	56	47	
Range	15–95	0–87	
Number of cases with *ALK* rearrangements	675 (3.1%)	201 (0.2%)	876 (0.8%)
Total number of ALK rearrangements	680	204	884
Fusions	615 (90.4%)	173 (84.8%)	788 (89.1%)
Other rearrangements	65 (9.6%)	31 (15.2%)	96 (10.9%)
EML4 fusion partner frequency	568 (83.5%)	63 (30.9%)	631 (71.4%)

Abbreviation: NSCLC, non-small cell lung cancer.

Table 2. Recurrent fusions partners in NSCLC and non-NSCLC samples

Non-NSCLC		NSCLC	
Partner	Count	Partner	Count
EML4	63	*EML4*	568
NPM1	16	*KIF5B*	7
STRN	16	*HIP1*	5
CLTC	9	*KLC1*	4
TNS1	9	*DCTN1*	3
ACTG2	5	*PRKAR1A*	3
IGFBP5	3	*STRN*	3
KIF5B	3	*CLTC*	2
SEC31A	3	*MPRIP*	2
TPM3	3		
AITC	2		
DCTN1	2		
PPP1CB	2		
TPM4	2		

Abbreviation: NSCLC, non-small cell lung cancer.

r*ALK* (Table 1). The lower frequency of high TMB in f*ALK*-positive NSCLC versus f*ALK*-positive non-NSCLC was significant ($p = .004$).

Multiple examples have been published of clinical responses to selected anti-ALK targeted therapy for patients whose non-NSCLC tumors harbor f*ALK* [12, 14, 16, 17, 19, 20, 22, 23, 26]. In this cohort of patients, novel examples of responses to ALK-targeted therapy include case Non-NSCLC 092, a non-Langerhans cell histiocytosis with a robust response to crizotinib (Figure 2), and Non-NSCLC 037, a renal cell carcinoma with a significant response to alectinib (Figure 3).

Figure 2 illustrates a prolonged, robust response to treatment with crizotinib for Non-NSCLC 092, a non-Langerhans cell histiocytosis. A 40-year-old male presented with severe interscapular pain. Magnetic resonance imaging (MRI) of the C-spine revealed a homogenous lesion in the cervical cord at C3-C4 measuring 2.5 × 1 × 1 cm with avid enhancement. This was thought to be neoplastic; hence, a CT scan of the thorax/abdomen/pelvis was obtained, which revealed heterogeneous enhancement of the hepatic parenchyma, numerous peritoneal and omental lesions, numerous osseous lesions (some of which were sclerotic whereas others were lytic), and scattered subcutaneous nodules. Comprehensive genomic profiling of a histiocytic biopsy sample from the liver revealed a *KIF5B-ALK* fusion. Based on the CGP results and the aggressive malignant clinical picture, treatment was started, which included cervical radiotherapy, one cycle of chemotherapy (cytoxan 750 mg/m^2, etoposide 100 mg/m^2 days 1–3, and prednisone 100 mg days 1–5), and finally crizotinib 250 mg daily from July 2015 to present. Comparison of a pretreatment positron emission tomography scan to scans obtained at 20 and 35 weeks shows a robust response to this crizotinib-based treatment regimen (Figure 2).

Successful targeting of an *ALK* fusion has also been achieved in the context of renal cell carcinoma (non-NSCLC 037), as illustrated by Figure 3. A 65-year-old male presented with a renal mass and pulmonary metastases. Nephrectomy was performed and pathology revealed a mixed histology in the renal specimen, comprising 70% papillary and 30% clear cell disease. The patient was initially treated with pazopanib but developed elevated transaminases. He then received an investigational MET inhibitor that was discontinued due to dermatologic toxicities. Following this course, he received everolimus with progression and development of interstitial changes consistent with pneumonitis. The patient was then placed on nivolumab with progression of new thyroid metastases, followed by cabozantinib. Within a short time frame, he was noted to have substantial headaches and hemorrhaging brain metastases were identified on MRI of the brain. Comprehensive genomic profiling evaluation of both circulating tumor DNA and a tissue biopsy of the kidney (October 2013) revealed an *EML4-ALK* translocation. He completed stereotactic radiotherapy to brain metastases, and then began therapy with alectinib. Both brain metastases and lung metastases displayed a substantial response to treatment. Shown here is a representative response in a mesenteric lymph node.

Discussion

The dramatic therapeutic benefit of therapies targeting ALK for patients with NSCLC driven by f*ALK* is now widely accepted. The ALK inhibitors crizotinib, ceritinib, and alectinib are all

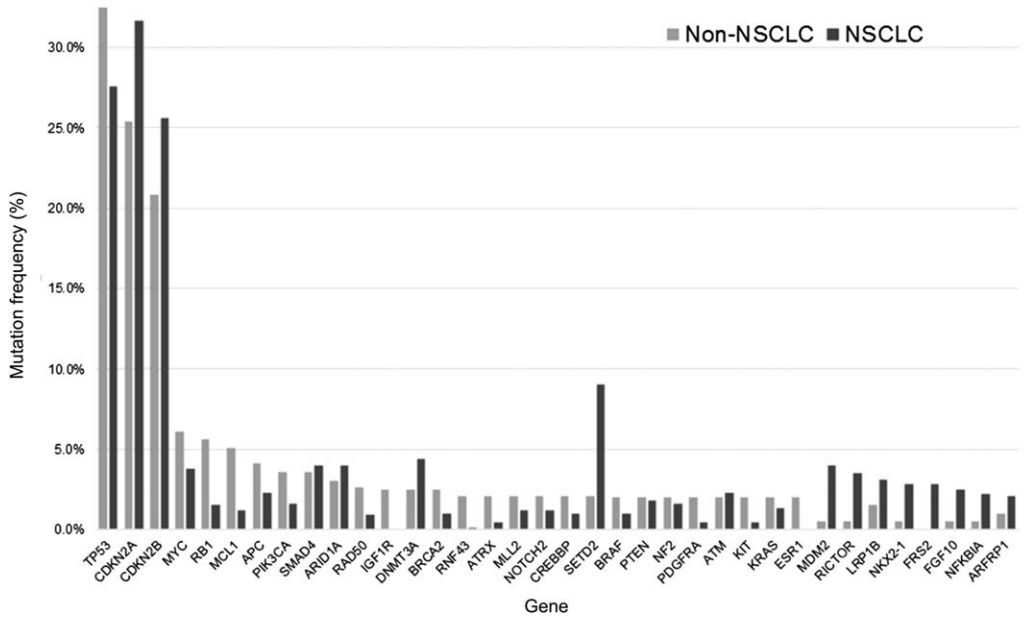

Figure 1. Mutation frequencies of genes coaltered with *ALK* fusions. Note that cases may have both *ALK* fusions and *ALK* nonfusion alterations in the same tumor. All cases feature at least a single *ALK* fusion genomic alteration.

Abbreviation: NSCLC, non-small cell lung cancer.

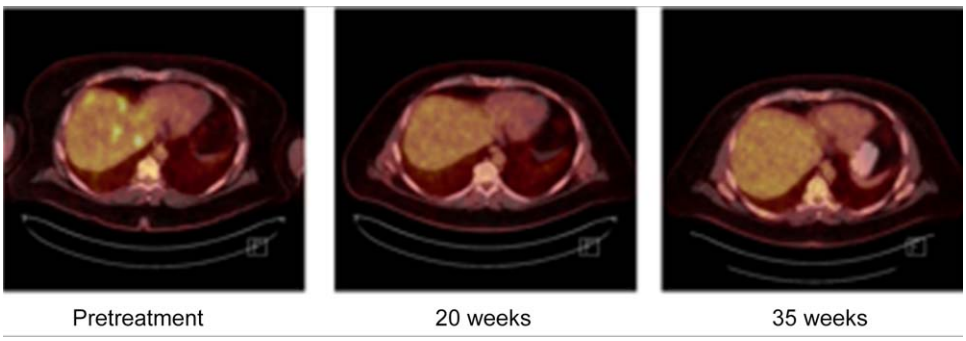

Figure 2. A series of positron emission tomography scans showing a robust and sustained response to a crizotinib-based treatment regimen. The patient received cervical radiotherapy, one cycle of chemotherapy (cytoxan 750 mg/m^2, etoposide 100 mg/m^2 days 1–3, and prednisone 100 mg days 1–5), and crizotinib 250 mg daily from July 2015 to present. Shown here are scans taken prior to treatment initiation (far left) and at 20 weeks (center) and 35 weeks (right) after treatment initiation.

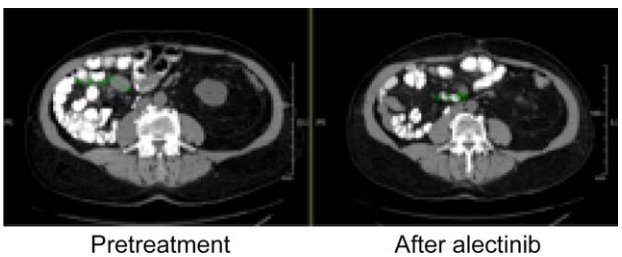

Figure 3. A representative response in a mesenteric lymph node to alectinib for a patient with renal cell carcinoma harboring an *EML4-ALK* fusion.

approved for the treatment of patients with NSCLC whose tumors test positive for *ALK* rearrangement [34, 35]. In addition, ALK inhibitors, including ceritinib, alectinib, brigatinib, and lorlatinib, are under evaluation for patients with *ALK*-rearranged NSCLC that may have developed resistance to crizotinib [34–36]. The *EML4-ALK* gene fusion has been observed in 3%–7% of NSCLC cases, more frequently in younger patients, nonsmokers, and men [37, 38]. As previously reported and seen in the present study, different *EML4-ALK* variants have been identified in a variety of both NSCLC and non-NSCLC cases, all of which contain the intracellular tyrosine kinase domain of *ALK* [39].

In this study of more than 114,000 clinical cases, f*ALK* are extremely uncommon in tumors other than NSCLC, with a frequency of only 0.2% in a series of more than 90,000 cases. These non-NSCLC, f*ALK*-driven tumors are significantly more often from female patients or younger patients, and less often have *EML4* as the *ALK* fusion partner, although the impact of fusion partner on the sensitivity to therapies remains under investigation [40]. In addition, this data shows that f*ALK* can be found in a wide variety of tumor types, including carcinomas, sarcomas, and hematolymphoid malignancies. Several of these tumor types warrant more detailed discussion. The presence of f*ALK* in tubular gastrointestinal cancers, especially colorectal cancer (CRC), is noteworthy, as are the diverse group of

unknown primary cases featuring fusions. In sarcomas, f*ALK* appear to segregate with smooth muscle differentiation. Finally, as expected, f*ALK* are more commonly identified in B-cell lymphomas compared with other hematological cancers (supplemental online Table 5).

ALK fusions were first identified in CRC in 2009 [41] using exon array profiling, and have been subsequently investigated by hybrid capture-based CGP [42] and indirectly detected by immunohistochemistry [43]. The 11 f*ALK*-positive CRC cases listed in supplementary online Table 2 represent only 0.1% of the more than 9,000 CRC cases profiled in this study. However, the clinical response to ceritinib treatment experienced by a patient with a *STRN-ALK* fusion [14] highlights that, however uncommon, the identification of an *ALK* fusion in a non-NSCLC tumor can lead to benefits from targeted therapy treatment [14]. Responses to the TRK/ALK/ROS1 inhibitor entrectinib have been reported for 2/2 CRC patients with ALK alterations in an ongoing phase 1/2 study [44] and for a patient whose CRC tumor harbored a novel *CAD-ALK* fusion [16]. Preclinical models involving established cell lines, patient-derived cell lines, and xenografts of f*ALK*-driven CRC have shown responsiveness to agents targeting ALK [45].

In the current study, 44 cases of cancer of unknown primary source (CUP) harbored f*ALK*. These tumors were classified as unknown primary site by the submitting clinician due to a lack of pulmonary involvement and/or insufficient pathology confirmation, such as being negative for TTF1 immunostaining. In this clinical context, the possibility of lung origin cannot always be discounted, and the finding of an *ALK* fusion to justify reclassification of CUP to an occult NSCLC is now well recognized [46]. The case Non-NSCLC 166 was submitted as a CUP with massive secondary pulmonary involvement and showed no expression of epithelial markers (cytokeratin, TTF1, etc.). Based on subsequent analysis, this tumor is likely a sarcoma and possibly a high-grade variant of inflammatory myofibroblastic tumor metastatic to the lung from a soft tissue origin [19]. Thus, for this CUP case, reclassification as a form of sarcoma appears warranted.

ALK fusions are identified in a variety of sarcomas, but are predominantly found in tumors with smooth muscle differentiation including leiomyosarcomas, epithelioid leiomyosarcomas, myxoid leiomyosarcomas, inflammatory myofibroblastic tumors, and smooth muscle tumors of uncertain malignant potential [20–23]. As seen in supplementary online Table 4, these smooth muscle sarcomas may be derived from soft tissues, including both superficial sites and deep sites such as the retroperitoneum, walls of the intestine, and the uterus. Evidence has also emerged that these *ALK* fusion driven sarcomas are responsive to both first-generation therapies, such as crizotinib, as well as second- and third-generation inhibitors [19–21].

ALK fusions were initially described in anaplastic large-cell lymphoma [1–5] and are generally restricted to large B-cell-type non-Hodgkin lymphoma (NHL), but are seen in the current study to occur in differentiated B-cell malignancies, such as myeloma, as well as histiocytic disorders [47]. *ALK*-driven B-cell malignancies are typically treated with standard chemotherapy plus, when indicated, anti-CD20 antibody infusion and bone marrow transplantation [48]. It is relatively uncommon for patients with NHL to receive anti-ALK targeted therapies, but recent evidence has emerged that chemorefractory f*ALK*-positive NHL is sensitive to inhibitors such as crizotinib [49].

The results of this study suggest that CGP may provide increased sensitivity for *ALK* fusion detection across a variety of tumor types. Recent evidence challenges the sensitivity of fluorescence in situ hybridization (FISH) as the standard of care for detecting f*ALK* in NSCLC [50], and although some investigators have suggested that the addition of immunohistochemistry screening (IHC) for ALK protein overexpression could prevent false-negative FISH results [51], IHC is prone to technical issues and the ability of IHC to detect all tumors driven by f*ALK* remains controversial. It should be noted that the non-NSCLC f*ALK*-driven cancers uncovered in the current study are significantly less likely to feature *EML4* as the *ALK* fusion partner and thus could present a greater challenge for detection if FISH were the only technique employed [50]. The CGP assay used in the current study detects all subtypes of *EML4-ALK* fusions, as well as f*ALK* with a wide range of non-*EML4* partners. Indeed, the first use of this assay in clinical practice was for a patient with widespread NSCLC, including brain metastases, whose tumor was negative for *ALK* fusion by FISH. Comprehensive genomic profiling detected an alternative *EML4-ALK* fusion and the treatment strategy was shifted from standard of care chemotherapy to anti-ALK targeted therapy. The patient achieved long-term durable disease control extending beyond 4 years [52, 53].

The inverse association between high TMB and the presence of an *ALK* fusion in both NSCLC and non-NSCLC is of potential interest when designing a precision therapy strategy for these patients. Tumor mutational burden calculated from CGP results has been directly linked to the efficacy of immune checkpoint-inhibitor drugs in NSCLC [54], urinary bladder urothelial carcinoma [33], and metastatic melanoma [55]. Although IHC-based analysis of programmed death-ligand 1 expression in the *ALK*-positive tumors presented in this study, both NSCLC and non-NSCLC, is not available, the observation that high TMB is rare in these patients suggests that immunotherapies may not be as broadly relevant compared with *ALK* fusion wild-type tumors.

Conclusion

ALK fusions can be identified in small sets of non-NSCLC patients and are found in a wide variety of epithelial and mesenchymal malignancies. The non-NSCLC cases harboring f*ALK* are more often identified in slightly older female patients, are more likely to have *ALK* fusion partners other than *EML4*, and are less likely to have high TMB than f*ALK*-negative malignancies. Initial evidence now strongly favors that anti-ALK therapies can be effective in a variety of tumor types driven by f*ALK* and further study in basket trials including various cancer types appears warranted.

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Disclosures

Jeffrey S. Ross: Foundation Medicine (E, RF, OI); **Siraj M. Ali**: Foundation Medicine (E, IP, OI); **Sumanta Pal**: Aveo, Bristol Myers Squibb, Exelixis, Genentech, Myriad Pharmaceuticals, Novartis, Pfizer (C/A) Astellas Pharma, Medivation, Novartis (H); **Julia A. Elvin**: Foundation Medicine (E, OI); **Alexa B. Schrock**: Foundation Medicine (E, OI); **James Suh**: Foundation Medicine (E, OI); **Christine E. Sheehan**: Foundation Medicine (C/A); **Jo-Anne Vergilio**: Foundation Medicine (E, OI); **Shakti Ramkissoon**: Foundation Medicine (E), Bristol-Myers Squibb (C/A); **Eric Severson**: Foundation Medicine (E, OI); **Sugganth Daniel**: Foundation Medicine (E, OI); **David Fabrizio**: Foundation Medicine, Juno Therapeutics, Seattle Genetics (OI), Foundation Medicine (E); **Garrett Frampton**: Foundation Medicine (E, OI); **Vince A. Miller**: Foundation Medicine (E, OI); **Philip J. Stephens**: Foundation Medicine (E, OI); **Laurie M. Gay**: Foundation Medicine (E, OI). The other authors indicated no financial relationships.

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See http://www.TheOncologist.com for supplemental material available online.

For Further Reading:

Yoko Shimada, Takashi Kohno, Hideki Ueno et al. An Oncogenic ALK Fusion and an RRAS Mutation in KRAS Mutation-Negative Pancreatic Ductal Adenocarcinoma. ***The Oncologist*** 2017;22:158–164; first published on February 6, 2017.

Implications for Practice:

The oncogenic DCTN1-ALK fusion and the RRAS mutation were associated with the development of pancreatic ductal adenocarcinoma (PDAC) in the absence of the KRAS mutation. Constitutional activation of DCTN1-ALK fusion protein was suppressed by the anaplastic lymphoma kinase tyrosine kinase inhibitors crizotinib and alectinib. Thus, a small subset of PDAC patients might benefit from therapy using these inhibitors.