

# Inflammatory Myofibroblastic Tumor Driven by Novel *NUMA1*-*ALK* Fusion Responds to *ALK* Inhibition

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## Abstract

Inflammatory myofibroblastic tumors (IMTs) are soft tissue neoplasms with rare metastatic potential. Approximately half of IMTs are positive for an *ALK* rearrangement, and *ALK* inhibitors have been used successfully in the treatment of IMTs with a variety of *ALK* fusions. This report describes a 21-year-old woman with an aggressive, metastatic IMT with a novel *NUMA1*-*ALK* fusion that showed a dramatic response to the *ALK* inhibitors crizotinib and alectinib. To our knowledge, this report provides the first published description of an IMT with a *NUMA1*-*ALK* fusion. The patient's aggressive IMT responded favorably to crizotinib and alectinib, suggesting that *ALK* inhibitors may be effective in IMT with *NUMA1*-*ALK* fusions. We review published reports of *ALK*-driven IMTs that have received *ALK* inhibitor therapy and suggest characteristics that may be associated with favorable response to treatment. We also discuss the strengths and limitations of immunohistochemistry, fluorescence in situ hybridization, and next-generation sequencing in the diagnosis and management of IMTs.

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Inflammatory myofibroblastic tumors (IMTs) are rare soft tissue neoplasms that usually arise in the lung, abdomen, or pelvis and affect primarily children and young adults.<sup>1</sup> IMTs are usually localized and metastatic disease is rare, accounting for <5% of all cases.<sup>2</sup> IMTs most often present with signs and symptoms restricted to the areas affected; however, 15% to 30% of people present with fever, weight loss, malaise, microcytic anemia, elevated erythrocyte sedimentation rate, thrombocytosis, or polyclonal hypergammaglobulinemia.<sup>3</sup> Although the histology of IMT is variable, tumors are generally composed of spindle cells in an inflamed stroma of plasma cells, lymphocytes, and eosinophils.<sup>2</sup> Surgery is the pri-

mary management modality; however, lesions may recur after surgical resection.<sup>2</sup>

Recent evidence suggests that the anaplastic lymphoma kinase (*ALK*) gene plays a role in the pathogenesis of some IMTs. *ALK* encodes a receptor tyrosine kinase normally expressed only in neural tissue,<sup>4</sup> and rearrangements of *ALK* can result in inappropriate activation of the *ALK* receptor tyrosine kinase.<sup>5</sup> Approximately half of IMTs are associated with an *ALK* gene rearrangement.<sup>6</sup> Fusions of *ALK* with *TPM3*, *TPM4*, *ATIC*, *CLTC*, *CARS*, *RANBP2*, *EML4*, and *SEC31L1* have been described previously.<sup>5,7</sup>

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ALK inhibitors have emerged as a successful therapy for ALK-associated IMT in both adult and pediatric patients.<sup>8-14</sup> To our knowledge, however, the response of IMT associated with a *NUMA1*-ALK fusion has never been documented. This report describes a 21-year-old patient with widely metastatic IMT with a *NUMA1*-ALK fusion who demonstrated a marked response to ALK inhibitor therapy. We then review published reports of ALK-driven IMT treated with ALK inhibitors and suggest predictors of favorable response to treatment.

## Case Description

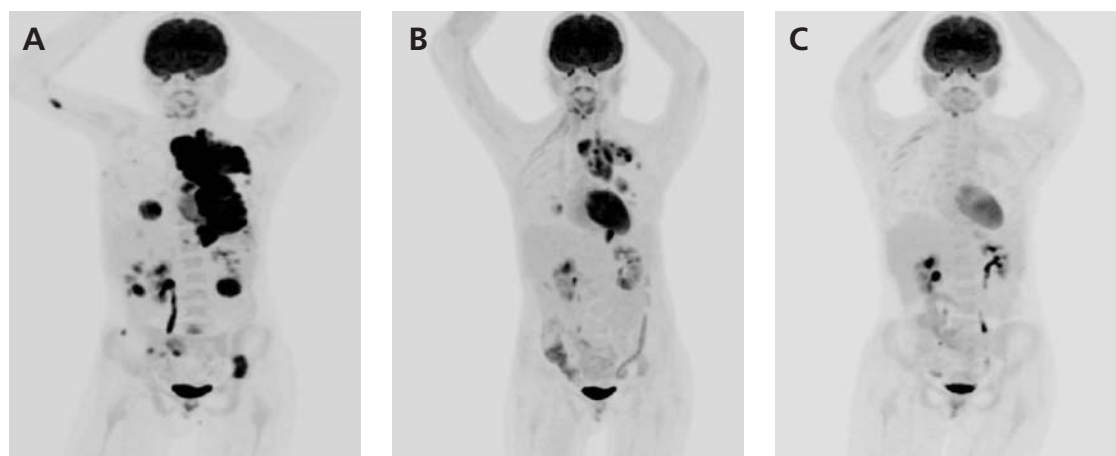
### Clinical Course

A 21-year-old woman initially presented with left shoulder pain and left arm swelling. She reported that she had experienced a 10- to 15-pound weight loss during the preceding year, a few months of fatigue and dry cough, and a few weeks of shortness of breath and dysphagia. She had also experienced intermittent night sweats and left-sided pleuritic chest pain, all of which had worsened acutely over the past month.

She was diagnosed with an acute deep vein thrombosis of her left internal jugular vein. On further evaluation, she was found to have a large mediastinal mass encasing multiple mediastinal structures and lesions involving the lungs, liver, spleen, kidney, bone, peritoneum, and iliacus muscle. A

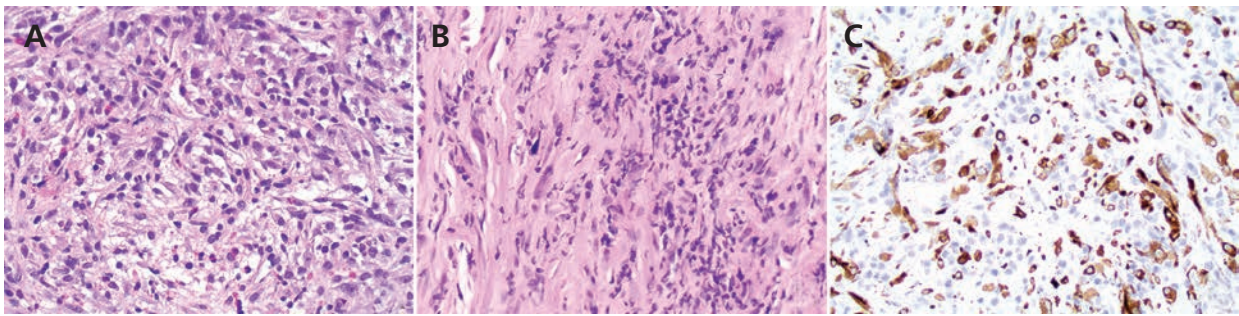
staging PET/CT scan showed multiple hypermetabolic lesions above and below the diaphragm, involving the mediastinum and left hemithorax, bilateral lungs, pleura, liver, left kidney, axial skeleton, and musculature (Figure 1A). Differential diagnosis at the time included lymphoma and metastatic germ cell tumor.

Biopsies of a lung mass and a left supraclavicular lymph node were performed. Histologic sections from both samples revealed a spindle cell proliferation that was variably cellular, with broad areas of fibrosis and obscuring lymphoplasmacytic infiltrates, without evidence of high-grade anaplastic features, coagulation tumor necrosis, or atypical mitotic figures (Figure 2). On immunohistochemistry (IHC), lesional cells showed unequivocal, strong, and diffuse reactivity for ALK (in a cytoplasmic and perinuclear pattern) and weak focal reactivity for smooth muscle actin and desmin. Other markers, including CD45, CD3, CD20, CD163, CD15, CD30, EBER, PAX5, pan cytokeratin-AE1/AE3, S100, and pan cytokeratin-MNF116, were negative. Plasma cells stained diffusely for both Kappa and Lambda with no evidence of light chain restriction. Fluorescence in situ hybridization (FISH) testing was reported as negative for *ALK* translocation; however, next-generation sequencing (NGS) by Foundation Medicine (Cambridge, MA) revealed a novel *NUMA1*-ALK fusion. The *ALK* translocation was detected on both DNA and RNA sequenc-



**Figure 1.** PET/CT demonstrating burden of disease. (A) At initial presentation, PET/CT demonstrated multiple hypermetabolic lesions above and below the diaphragm involving the mediastinum, bilateral lungs, left pleura, liver, left kidney, abdomen, axial skeleton, and musculature (maximum standardized uptake value [ $SUV_{max}$ ], 48.7). (B) One month after crizotinib therapy initiation, PET/CT demonstrated reduced size and FDG avidity of several hypermetabolic masses/lesions involving the lung/pleura, liver, and bone, as well as the left perinephric region ( $SUV_{max}$ , 14.1). (C) After 6 months of crizotinib therapy, patient was switched from crizotinib to alectinib for concern for possible contribution of crizotinib to her pneumonitis. A PET/CT performed one month after beginning alectinib demonstrated further reduction in FDG avidity of neck, chest, and bone lesions ( $SUV_{max}$ , 1.9).

## NUMA1-ALK IMT Responds to ALK Inhibition



**Figure 2.** Histology sections from biopsy samples. (A) Sections showing a banal spindle cell proliferation in swirling growth pattern punctuated with sprinkling of chronic inflammatory cells and eosinophils (hematoxylin-eosin, original magnification x200). (B) High power view showing areas with obscuring lymphoplasmacytic infiltrates (hematoxylin-eosin, original magnification x400). (C) Lesional cells demonstrating diffuse and strong ALK reactivity (ALK, original magnification x400).

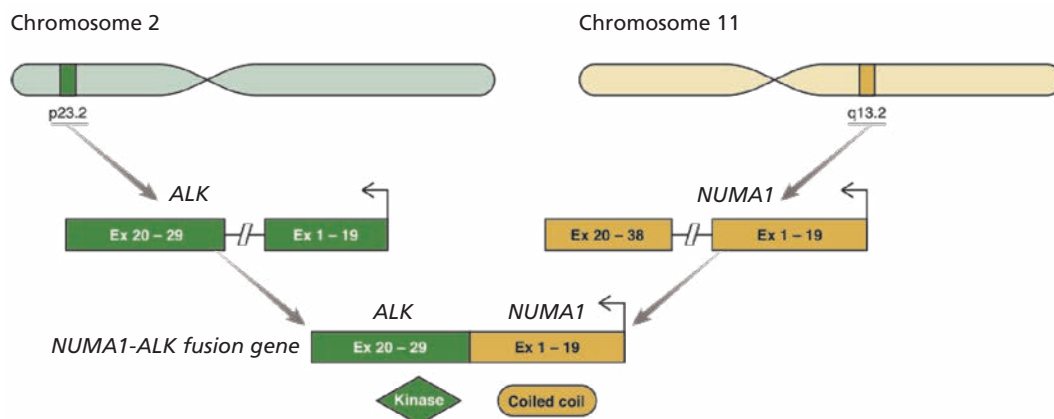
ing analyses. The following fusion was discovered: 5'-NUMA1(ex1-19 NM\_006185)-ALK(ex20-29 NM\_004304) (Figure 3). The depth of sequencing was adequate, with a 755 median exon depth for the whole specimen. Taken together, these results were consistent with an ALK-driven IMT.

When the patient was scheduled to begin therapy, NGS results were still pending. Given the strong reactivity for ALK by IHC, she was started on crizotinib, 250 mg twice daily. At 2-week follow-up, the patient's symptoms had markedly improved: her dry cough had resolved, she felt less pressure in her chest, and she was able to eat and swallow pills. Apart from lower-abdominal cramping, which was controlled with hyoscyamine, she tolerated crizotinib therapy well.

Four weeks after beginning crizotinib, a restaging PET scan showed pronounced improvement, with reductions in size and FDG avidity of multiple hypermetabolic masses involving the lung, pleura, liver, left perinephric region, and osseous lesions

(Figure 1B). Improvement was specifically noted in a left lower lobe mass (maximum standard uptake value [ $SUV_{max}$ ] decreased from 48.7 to 14.1), right lower lobe lesion ( $SUV_{max}$ , 17.7 to 6.6), left kidney mass ( $SUV_{max}$ , 16.7 to 8.0), and right sacral lesion ( $SUV_{max}$ , 12.4 to 4.2).

Six weeks after beginning crizotinib, nivolumab at 3 mg/kg intravenously every 2 weeks was added to her regimen given evidence of high-positive PD-1 expression in tumor-infiltrating lymphocytes (>25%, clone NAT105 by Cell Marque; Rocklin, CA). She received 12 weeks of combination therapy with crizotinib and nivolumab with continued radiographic response to therapy. However, she developed grade 2 pneumonitis and grade 3 transaminitis, suspected to be related to nivolumab and possibly to crizotinib. Both agents were held and she was treated with prednisone, 1 mg/kg/d, after which she experienced rapid improvement in her pneumonitis and normalization of her transaminases. Prednisone was tapered slowly over 6 weeks and crizotinib was



**Figure 3.** Illustration of the NUMA1-ALK fusion.

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**Table 1. Adult and Pediatric Cases of ALK-Driven IMTs Treated With ALK Inhibitors**

Study	ALK-Fusion	Age, y	Sex	Organ Involvement	Pathology Features, General	ALK Localization	Prior Systemic Therapies	ALK Inhibitor	Response/ Management
Butrynski et al, <sup>11</sup> 2010	<i>RANBP2-ALK</i>	44	M	Ascites, RUQ mass, omental caking	Mostly epithelioid cells with large vesicular nuclei, prominent nucleoli, amphophilic cytoplasm, embedded in a myxoid stroma; neutrophilic infiltrate	Nuclear membrane	Tumor debulking; hyperthermic peritoneal perfusion of cisplatin, doxorubicin, mitomycin C; doxorubicin and ifosfamide followed by imatinib maintenance therapy	Crizotinib	Partial response at 2 months; progression noted 7 months after starting therapy; patient underwent surgical debulking and crizotinib dose increased; complete remission at 30 months
Gaudichon et al, <sup>9</sup> 2016	<i>EML4-ALK</i>	16	F	Left shoulder mass	Elongated spindle cells with amphophilic cytoplasm, centered on enlarged and moderately atypical nuclei harboring fine chromatin and small nucleoli, limited mitotic activity, lymphoid inflammatory infiltrate	Not specified	NSAIDs, steroids, vinblastine, vincristine, actinomycin-D, cyclophosphamide, vinorelbine, methotrexate; palliative external beam radiotherapy	Crizotinib	30% volume reduction within a few weeks of starting treatment; intracranial lesions required radiotherapy; complete remission 3 years after starting treatment
Jacob et al, <sup>10</sup> 2014	Not described	45	F	Multiple liver masses, lesions in the lumbar spine	Spindle cell proliferation, inflammatory infiltrate of lymphocytes, plasma cells, histiocytes, and eosinophils; no necrosis or atypical mitoses	Cytoplasmic	None	Crizotinib	Complete remission at 27-month follow-up
Kimbara et al, <sup>22</sup> 2014	<i>RANBP2-ALK</i>	22	M	Pelvic tumor with invasion of distal ileum, ascites	Predominately polygonal tumor cells with distinct nucleoli and eosinophilic cytoplasm; minor spindle cell component; nuclear atypia, mitotic figures; necrosis; predominately neutrophil infiltrate	Nuclear membrane	Two surgical excisions, doxorubicin	Crizotinib	Tumor shrinkage 1 month after starting therapy; complete remission at 10 months after starting therapy
Kiratli et al, <sup>12</sup> 2016	Not described	7	F	Right eye mass	Hyalinized connective tissue with spindle cells; infiltrate of lymphocytes, plasma cells, and histiocytes; Ki-67 proliferation index of 5%	Cytoplasmic	None	Crizotinib	Complete remission at 12 months; crizotinib held but patient with recurrent disease within 3 months; crizotinib restarted; complete remission 14 months after starting second course of crizotinib therapy
Liu et al, <sup>23</sup> 2015	<i>RANBP2-ALK</i>	22	M	Right abdominal mass, enlarged lymph nodes	Many cell types, varied structure; rounded, epithelioid cells with round, vesicular nuclei, large nucleoli, and amphophilic cytoplasm; spindle cell component; mitotic activity 1–5 per HPF; inflammatory infiltrate, predominantly neutrophils; focal necrosis	Cytoplasmic and perinuclear	Surgical excision	Crizotinib	Complete remission at 16 months

(continued on next page)

Abbreviations: ARDS, acute respiratory distress syndrome; BSO, bilateral salpingo-oophorectomy; F, female; HPF, high-power field; IMT, inflammatory myofibroblastic tumor; M, male; NSAID, nonsteroidal anti-inflammatory drug; RUQ, right upper quadrant.

resumed after a 4-week break. However, because of recurrent pneumonitis 3 weeks after resuming crizotinib, a decision was made to transition to alectinib to exclude the possibility that crizotinib was contributing to her pulmonary symptoms. Her pneumonitis and transaminitis resolved with the change to alectinib and with a second course of prednisone. At the time of writing, she continues to do well clinically, with evidence of a near complete response on staging studies at 13 months (Figure 1C).

**Discussion**

This study is the first to our knowledge to describe the *NUMA1-ALK* fusion in IMT and demonstrate the effectiveness of the ALK inhibitors, crizotinib and alectinib, in the management of this IMT variant.

The *NUMA1-ALK* fusion has not been previously documented in public databases, including The Cancer Genome Atlas (TCGA), the International Cancer Genome Consortium (ICGC), and the Catalogue of Somatic Mutations in Cancer (COSMIC).

## NUMA1-ALK IMT Responds to ALK Inhibition

Table 1. Adult and Pediatric Cases of ALK-Driven IMTs Treated With ALK Inhibitors (cont.)

Study	ALK-Fusion	Age, y	Sex	Organ Involvement	Pathology Features, General	ALK Localization	Prior Systemic Therapies	ALK Inhibitor	Response/Management
Lorenzi et al, <sup>8</sup> 2014	CLTC-ALK	24	M	Multiple abdominal masses, including a liver mass	Spindle cells with ovoid nuclei containing prominent nucleoli and eosinophilic cytoplasm; inflammatory infiltrate with lymphocytes, neutrophils, eosinophils, and plasma cells; minute necrotic foci, mitotic index of 7 mitoses/10 HPF; Ki67 index 10%	Cytoplasmic (granular)	Surgery, without resection of hepatic mass	Crizotinib	Stable disease 4 months after starting treatment
Mansfield et al, <sup>16</sup> 2016	TPM3-ALK	32	M	Tumor involving left lung and chest wall, medial right thigh, right gluteal muscle and omentum	Myofibroproliferation with inflammatory infiltrate of plasma cells and eosinophils	Not described	Prednisone	Crizotinib	Partial response, but subsequent disease progression after 8 months; treated with celecoxib – further progression; then started on ceritinib 750 mg daily, reduced to 600 mg daily after developing nausea; partial response to ceritinib after 8 weeks of treatment; recurrence noted at 18 months
Ono et al, <sup>27</sup> 2016	RANBP2-ALK	57	M	Right intrapleural lesion, chest wall invasion, mediastinal lymph node metastasis, pleural dissemination	Not described	Not described	ASP3026, 125 mg once daily	Ceritinib	Partial response at 6 months after starting ceritinib; disease progression at 11 months after starting ceritinib; crizotinib, cisplatin, pemetrexed given – no tumor response; received palliative radiation, whole-brain radiation; patient died
Shash et al, <sup>28</sup> 2016	TPM3-ALK	8	F	Left lower lobe lung mass	Heterogenous with myofibroblastic spindle cells, and polygonal cells with prominent nucleoli and atypical mitotic figures; inflammatory infiltrate of lymphocytes, neutrophils, and plasma cells; extensive necrosis, lymphovascular invasion	Cytoplasmic	Surgical resection	Crizotinib	Minimal FDG uptake after 3 months of therapy; patient died of ARDS 4 months after starting crizotinib therapy, but no evidence of IMT tumor at time of death
Subbiah et al, <sup>13</sup> 2015	DCTN1-ALK	≈50	F	Uterine mass	Not described	Not described	Surgical resection (BSO, pelvic lymphadenectomy, omentectomy)	Crizotinib and pazopanib	Partial response after two 21-day cycles of therapy; partial remission 6 months after starting therapy
Present study	NUMA1-ALK	21	F	Tumor involving the mediastinum and left hemithorax, bilateral lungs, pleura, liver, spleen, peritoneum, left kidney, axial skeleton, and iliacus muscle	Spindle cell proliferation with broad areas of fibrosis and obscuring lymphoplasmacytic infiltrates, without evidence of high-grade anaplastic features, coagulation tumor necrosis, or atypical mitotic figures	Cytoplasmic and perinuclear	None	Crizotinib and alectinib	Near complete response on staging studies at 7 months

Abbreviations: ARDS, acute respiratory distress syndrome; BSO, bilateral salpingo-oophorectomy; F, female; HPF, high-power field; IMT, inflammatory myofibroblastic tumor; M, male; NSAID, nonsteroidal anti-inflammatory drug; RUQ, right upper quadrant.

However, numerous other ALK fusions have been recorded in the context of IMTs<sup>5</sup> and are thought to drive tumor formation by activating the ALK tyrosine kinase, a member of the insulin receptor family.<sup>15</sup> ALK-positive IMTs have previously demonstrated an excellent response to ALK inhibitors such as crizotinib<sup>8–13</sup> and ceritinib.<sup>14</sup> In the present case, an IMT with a novel NUMA1-ALK fusion also demonstrated a marked initial response to crizotinib, and ongoing response to the second-generation ALK inhibitor alectinib.

The fact that our patient had metastatic disease despite the absence of high-grade anaplastic features and necrosis on histology was not unprecedented; favorable histologic characteristics do not necessarily predict a favorable clinical course in IMT.<sup>16</sup> However, ALK positivity usually predicts localized disease<sup>16–18</sup> with the exception of the epithelioid variant of IMT, driven by the RANBP2-ALK or RRBPI-ALK fusions.<sup>19,20</sup> Epithelioid inflammatory myofibroblastic sarcoma, in contrast to most IMTs that demonstrate ALK staining in a cytoplasmic pattern,<sup>1</sup> demon-



strates ALK staining in a nuclear membrane or perinuclear pattern.<sup>19</sup> Interestingly, our patient's tumor also showed ALK reactivity in a perinuclear pattern, likely reflecting the nuclear localization of the nuclear mitotic apparatus (NUMA) protein, which contributes to chromosome separation and nuclear rebuilding during cell division.<sup>21</sup>

In cases of ALK-driven IMT treated with ALK inhibitors, our review of the literature demonstrated no obvious association between histologic features and response to ALK inhibitor therapy (Table 1). Abdominal organ involvement rather than lung involvement at presentation may also be associated with a more favorable response to ALK inhibitor therapy. All cases initially involving abdominal organs showed either complete remission 10 to 30 months after starting therapy (4/5 patients)<sup>10,11,22,23</sup> or stable disease 4 months after starting therapy (1/5 patients).<sup>8</sup> In contrast, 3 of 4 cases with initial lung involvement demonstrated poor outcomes with ALK inhibitor therapy: 2 were characterized by disease progression at 8 and 11 months,<sup>24,25</sup> and 1 patient with pulmonary involvement died of acute respiratory distress syndrome 4 months into treatment despite marked radiographic response to crizotinib.<sup>26</sup> More data are needed to definitively compare abdominal and pulmonary IMT and the potential role of tumor microenvironment on ALK inhibitor response. We note that disease progression on prior ALK inhibitor therapy is, not surprisingly, associated with poor response to subsequent ALK inhibition: both cases in our literature review showed rapid disease progression (Table 1).<sup>24,25</sup>

The present study highlights the strengths and limitations of IHC, FISH, and NGS in the diagnosis and management of IMTs. Our false-negative FISH

results may have arisen from a conservative threshold for positivity, incorrect probe hybridization, DNA folding, nuclear sectioning, or tumor heterogeneity.<sup>27,28</sup> Ambiguity regarding ALK reactivity can prevent the timely use of ALK inhibitors effective against ALK-positive IMT; IHC showing ALK reactivity may be sufficient grounds to initiate treatment with ALK inhibitors.<sup>9</sup> However, NGS may help resolve discrepancies between IHC and FISH in the process of diagnosing IMT.

## Conclusions

This report presents a 21-year-old woman with widely metastatic IMT driven by a novel *NUMA1-ALK* fusion. Although the ultimate durability of her response is unknown and the emergence of resistance to ALK inhibitors is well described in other ALK-related malignancies,<sup>29</sup> treatment with the ALK inhibitors crizotinib and alectinib has thus far led to a deep and sustained response of  $\geq 13$  months. Notably, this therapy was initiated at a comprehensive cancer center with experience managing IMTs; we strongly recommend multidisciplinary evaluation at an experienced center for all patients with newly diagnosed IMTs, and encourage all centers that engage in the treatment of IMTs to pursue prospective collection of clinical disease features, coupled with comprehensive molecular characterization of tumors,<sup>30</sup> with the goal of characterizing the full spectrum of oncogene fusions in IMT, determining the prognosis associated with each variant, and predicting the response of each variant to kinase inhibitor therapy. Sharing these data through existing cancer databases (ClinicalTrials.gov identifier: NCT02677961) will be essential for progress in managing this disease.<sup>31,32</sup>

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