case reports

STRN-ALK Fusion in a Case of Malignant Peritoneal Mesothelioma: Mixed Response to Crizotinib, Mode of Resistance, and Brigatinib Sequential Therapy

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Introduction

ALK fusions were first described by Morris et al[1] in 1994. Several studies have reported genetic alterations of the *ALK* gene in various tumor types since then, consisting of mutations, amplifications, and fusions.[1-3] Fusion proteins have an active C-terminal tyrosine kinase domain in common.[3] Here, we describe an *STRN-ALK* fusion in malignant peritoneal mesothelioma (MPM), which has previously been documented in other neoplasms, including thyroid cancer, renal carcinoma, leukemia, lymphoma, colon adenocarcinoma, head and neck adenocarcinoma, pericardial and peritoneal mesothelioma, and cutaneous squamous cell carcinoma.[4-6]

MPM is a rare disease with an incidence of approximately seven per million people per year.[7] Patients' life expectancy is low (on average 12 months) because of the late clinical presentation with abdominal or pelvic pain or lymphadenopathy.[8,9] Recently, *ALK* rearrangements have gained attention, especially in young female patients with MPM. Hung et al[10] identified three *ALK* fusions in 88 consecutively screened patients with MPM. Fusion partners were *ATG16L1*, *TPM1*, and *STRN*. In another study by Mian et al,[11] among 32 patients ≤ 40 years old with mesothelioma (of which 25 were MPM), an *ALK* rearrangement was detected by fluorescence in situ hybridization in two patients (6%). One of the cases harbored an *STRN-ALK* fusion as described in the current case. Argani et al[12] described additional five cases of *ALK* fusions in pediatric MPM. Subsequently, three more cases of *STRN-ALK* rearrangements in MPM have been published individually.[6,13,14]

In non–small-cell lung cancer (NSCLC), the discovery of specific drugs targeting *ALK* rearrangements led to significant therapeutic advances. Currently, various ALK inhibitors, namely, ceritinib, crizotinib, and alectinib, are used as first-line treatment in adult *ALK*-positive advanced NSCLC. Although crizotinib as a first-generation ALK inhibitor has already proven superiority over chemotherapy,[15] next-generation ALK inhibitors such as ceritinib yielded even better survival rates.[16] Moreover, both brigatinib and alectinib demonstrated superior effectiveness when directly compared with crizotinib.[17,18] Unfortunately, resistance is frequently observed following an initial response in all these agents.[19] Mechanisms of resistance, which often include ALK mutations, are in general universal although variable mutational frequencies are observed depending on the inhibitor.[20]

Despite this large base of knowledge for lung cancer, the evaluation of *ALK* fusions in other entities remains challenging because of limited available data.

Case Report

In April 2019, a 24-year-old woman presented with pain in the lower abdomen, a recently diagnosed deep vein thrombosis, and intentional weight loss of 20 kg in 9 months. Transvaginal sonography and magnetic resonance imaging revealed a 16 cm measuring cystic solid tumor in the Douglas cavity (Fig 1A). On histopathologic examination, the tumor displayed an epithelioid component with papillary morphology and an admixed sarcomatous part. Tumor cells were weakly positive for pan-cytokeratin (clones AE1/AE3), p53, WT1, PAX8, estrogen receptor, EMA, and CAM5.2, while being negative for inhibin and TTF1. The Ki67 index was 20%. Initially, the tumor was diagnosed as a high-grade serous ovarian carcinoma with sarcomatous dedifferentiation. The diagnosis was later revised and changed to a biphasic malignant peritoneal mesothelioma prompted by the unexpected results of next-generation sequencing. Indeed, additional immunohistochemical analyses showed that the tumor was positive for CK5/6 and CK7 with predominant staining in the epithelioid component. Also, D2-40 was especially positive in the sarcomatoid part and displayed a cap-like membranous positivity in the epithelioid area. Calretinin staining was considered negative since only slight focal nuclear immunoreactivity was observed, and the cytoplasmic reactivity should not be counted. Ber-EP4 was completely negative (Figs 1B-1G).

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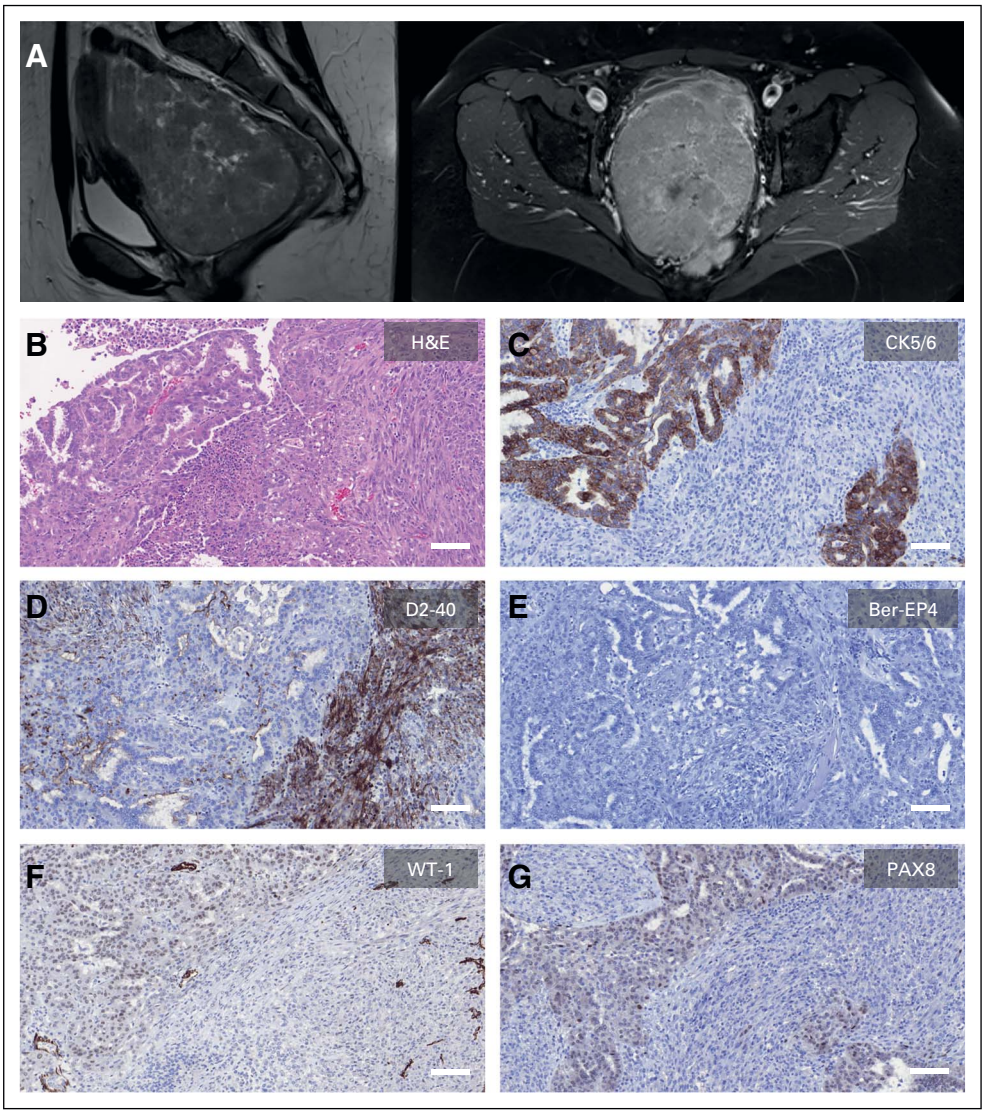

FIG 1. Immunohistochemical characterization of the resected tumor: (A) magnetic resonance imaging showing a large inhomogeneous pelvic mass with sharply delineated tumor borders and mild contrast enhancement (malignant peritoneal mesothelioma); left panel: sagittal T2-weighted image and right panel: contrast-enhanced transversal T1-weighted section with fat saturation; (B) section of the H&E stained tumor on the ovarian surface displaying a biphasic growth pattern with papillary epithelioid and sarcomatoid morphology; (C) CK5/6 immunohistochemistry was positive in the epithelioid component; (D) D2-40 immunohistochemistry exhibiting diffuse positivity in the sarcomatoid and a cap-like focal positivity in the epithelioid component; (E) Ber-EP4 was negative; (F) WT-1 reacted positive in the tumor nuclei; and (G) PAX-8 was predominantly positive in the epithelioid areas. Scale bars: 100 μm. H&E, hematoxylin and eosin; WT, wild type.

Staging contrast-enhanced computed tomography (CT) revealed pathologic lymph nodes in the left axilla and the lower anterior mediastinum and peritoneal dissemination. Hysterectomy and tumor debulking with the removal of the peritoneal nodes were performed.

Chemotherapy with paclitaxel (175 mg/m^2, once every 3 weeks [q3w]) and carboplatin (AUC5, q3w) was applied for five cycles starting in May 2019, which were replaced by pegylated liposomal doxorubicin (PEG)-doxorubicin (30 mg/m^2 q3w) and trabectedin (1.1 mg/m^2 q3w) in September 2019. In November 2019, the general conditions of the patient worsened and several metastases in the abdominal wall showed further growth. On November 12, a core needle biopsy of the scar tissue metastasis was performed. The use of the FusionPlex Lung Kit (Archer) on a MiSeq platform (Illumina) led to the discovery of an *STRN-ALK* fusion sequence (*STRN* (NM_003162.3) Exon3 and *ALK* (NM_004304.4) Exon20). Subsequent analyses also detected the fusion transcript in the primary resection specimen. Fluorescence in situ hybridization using the ZytoLight SPEC *ALK/EML4* TriCheck Probe (ZytoVision) confirmed the fusion event, consisting of one fused and a single red signal in most tumor cells, described as a positive break-apart pattern by the manufacturer. In concordance with the detected fusion gene, ALK immunohistochemistry was strongly positive (Fig 2).

In December 2019, treatment with the ALK inhibitor crizotinib was started at a dose of 250 mg twice daily. Soon after, the patient experienced relief in her severe pain as well as fatigue and nausea. As the last cycle of PEG-doxorubicin had been applied more than 6 weeks before change of treatment, the improvement of symptoms was not attributed to the end of chemotherapy but rather to the initiation of crizotinib treatment. A follow-up CT scan performed 2 months after starting crizotinib therapy showed a partial response with pronounced tumor shrinkage at most tumor locations. The tumor marker cancer antigen 12-5 was within the limit for the first time (22.5 U/mL, normal

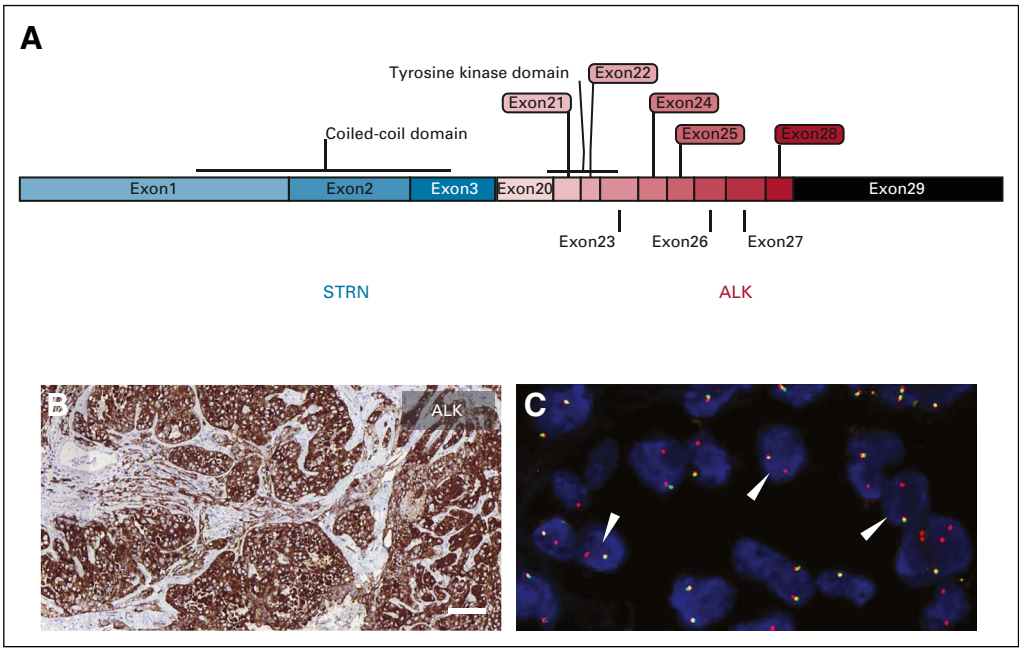

FIG 2. Functional characterization of the *STRN-ALK* fusion: (A) schematic representation of the detected *STRN-ALK* fusion; (B) diffusely strong immunohistochemical ALK positivity in both tumor components of the primary resection specimen; scale bar: 100 μm; and (C) fluorescence in situ hybridization break apart with one red-green fused and one red signal (exemplary white arrow heads) in 68% of tumor cells, which is described as a positive break-apart pattern by the manufacturer.

range < 35 U/mL). However, a new lesion measuring 9 × 4 cm occurred in the pelvis, causing urinary flow obstruction and hydronephrosis. After ureteric stent implantation, the patient was completely free of symptoms and creatine levels normalized. The possibility of testing the new lesion by CT-guided biopsy was discussed with the patient, but finally declined after risk disclosure. Since crizotinib treatment was still very well-tolerated, the therapy was continued for 2 more months (Fig 3).

In April 2020, liver metastases occurred. The pelvic tumor and the metastasis in the scar tissue and retroperitoneal lymph nodes were constant in size. The patient's condition worsened, and repeated blood transfusions because of symptomatic anemia were administered. A CT scan in June 2020 showed further progression, with an emphasis on the subcutaneous metastasis in the median laparotomy scar.

Subsequently, a core needle biopsy of the progressive abdominal wall metastasis was taken in June 2020. The biopsied material harbored a secondary *ALK* gene mutation (c.3586C>A and p.L1196M), detected by next-generation DNA sequencing after hybrid capture–based DNA enrichment and library generation using the TSO500 (Illumina) panel on a NextSeq sequencing platform (Illumina). The identified alteration is an oncogenic missense mutation previously described and associated with resistance to crizotinib treatment in NSCLC.[21] To assess the functional effect of the observed resistance mutation, we determined the levels of canonical ALK targets, such as total extracellular signal–regulated kinases 1 and 2 (ERK1/2), phosphorylated or activated mammalian target of rapamycin (p-mTOR), signal transducer and activator of transcription 3 (p-STAT3), and total B-cell lymphoma-extra large (Bcl-XL), by immunohistochemistry of tumor biopsies before and during crizotinib treatment. Activation of ALK downstream effectors was equally strong in both settings, implying persistent ALK activity under crizotinib therapy and, thereby, treatment resistance (Fig 4A). The results were discussed in the molecular tumor board. Treatment with brigatinib, a second-generation ALK inhibitor, was recommended and initiated in July 2020 (90 mg once daily for 7 days and afterward 180 mg once daily). A CT scan in August 2020 yielded a mixed response: regression in size of parailiacal soft tissue metastases, pelvic metastases, and the abdominal wall's biopsied metastasis was detected (Fig 4B), whereas pulmonary metastases remained constant in number and diameter. However, multiple new hepatic and splenic metastases were detected.

By the end of August 2020, the patient's condition deteriorated. Laboratory diagnostics demonstrated severe hyperglycemia (CTCAE grade 4, 757 mg/dL at admission) and hyperkalemia (5.9 nmol/L), attributed to the brigatinib therapy. Also, a gallbladder empyema was diagnosed, which was treated by antibiotic therapy with piperacillin and tazobactam with a complicating Clostridium difficile colitis. The patient passed away in September 2020.

The study was conducted according to the Declaration of Helsinki's guidelines and approved by the Ethics Committee

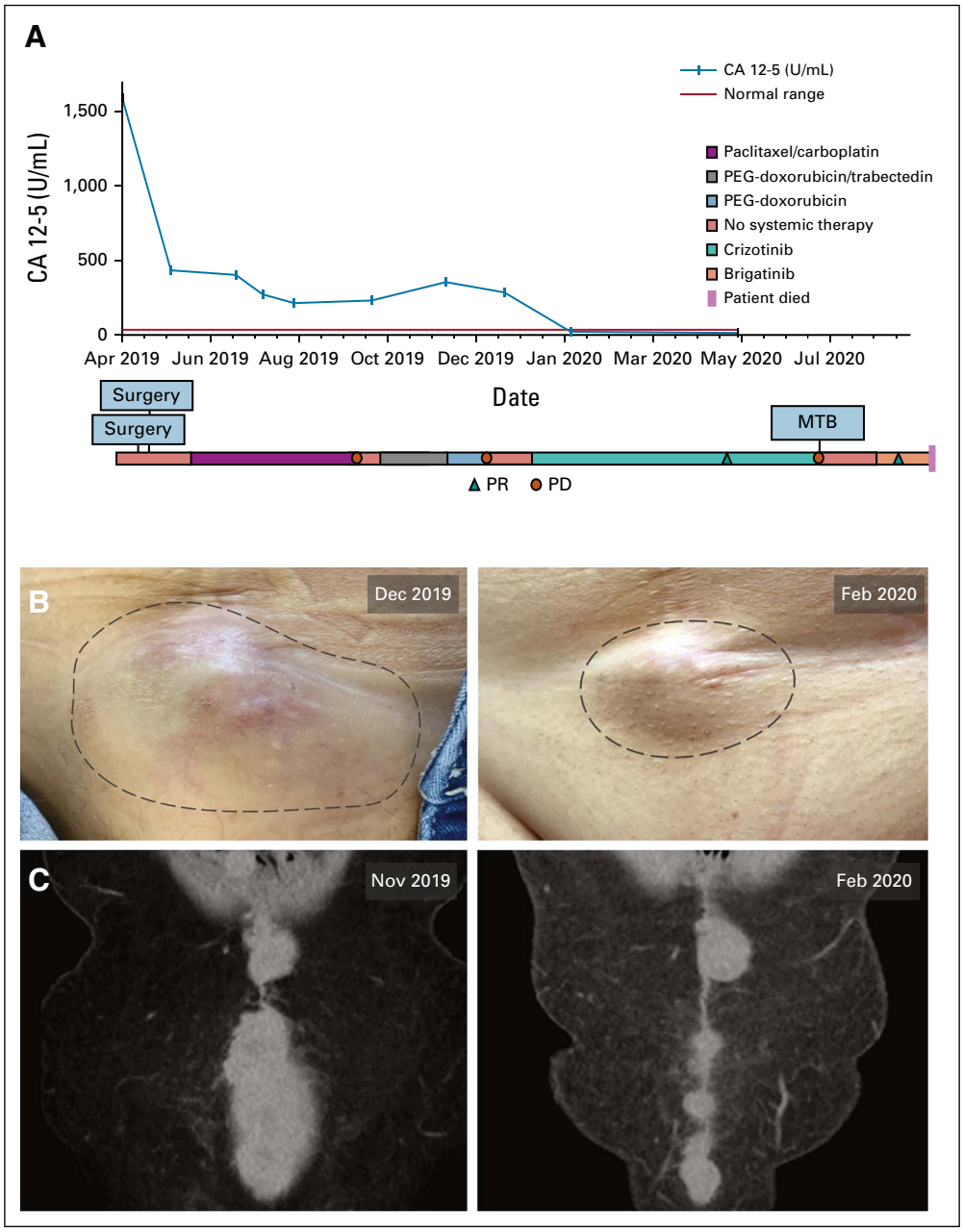

FIG 3. Targeted therapy with crizotinib: (A) overview of the clinical course with a graphical representation of CA 12-5 values over time and corresponding therapy; (B) photodocumentation of a subcutaneous metastasis in the median laparotomy scar before crizotinib therapy in December 2019 (left panel) and February 2020 under crizotinib therapy (right panel); and (C) coronal reformations of contrast-enhanced computed tomography showing a significant reduction of the abdominal wall tumor before (left panel) and during treatment with crizotinib (right panel). CA 12-5, cancer antigen 12-5; MTB, molecular tumor board; PEG, pegylated-liposomal; PD, progressive disease; PR, partial response.

of the University of Regensburg (Molecular Tumor Board Registry Study, protocol code 20-1682-101).

Written informed consent was obtained from the patient.

Discussion

Only anecdotal reports on targeted treatments for MPM with confirmed *ALK* fusions exist. One case report describes a dramatic response of a 13-year-old female patient suffering from MPM with a confirmed STRN-ALK fusion, who experienced a marked reduction in tumor volume within 3 months of treatment with ceritinib.[22] By contrast, another case of a 9-year-old female pediatric patient with an *STRN-ALK* fusion MPM did not benefit from crizotinib therapy.[12] In a third recent case report, crizotinib combined with cisplatin and gemcitabine was used to treat a 5-year-old chemotherapy-refractory pediatric patient, who achieved a complete remission lasting for at least 3 years.[14] A drug screening approach of primary MPM-patient-derived cancer cells revealed their sensitivity to various ALK, MEK, and ERK inhibitors and the synergistic antigrowth effect of combining ALK inhibitors with MEK and PI3K/mTOR inhibitors.[14]

In the case reported here, the effect of crizotinib treatment lasted for about 3 months until a mixed response in the different tumor sites and a new pelvic tumor manifestation and hepatic metastases occurred. Notably, to our knowledge, this is the first time an ensuing resistance mutation (p. L1196M *ALK*) has been detected and functionally

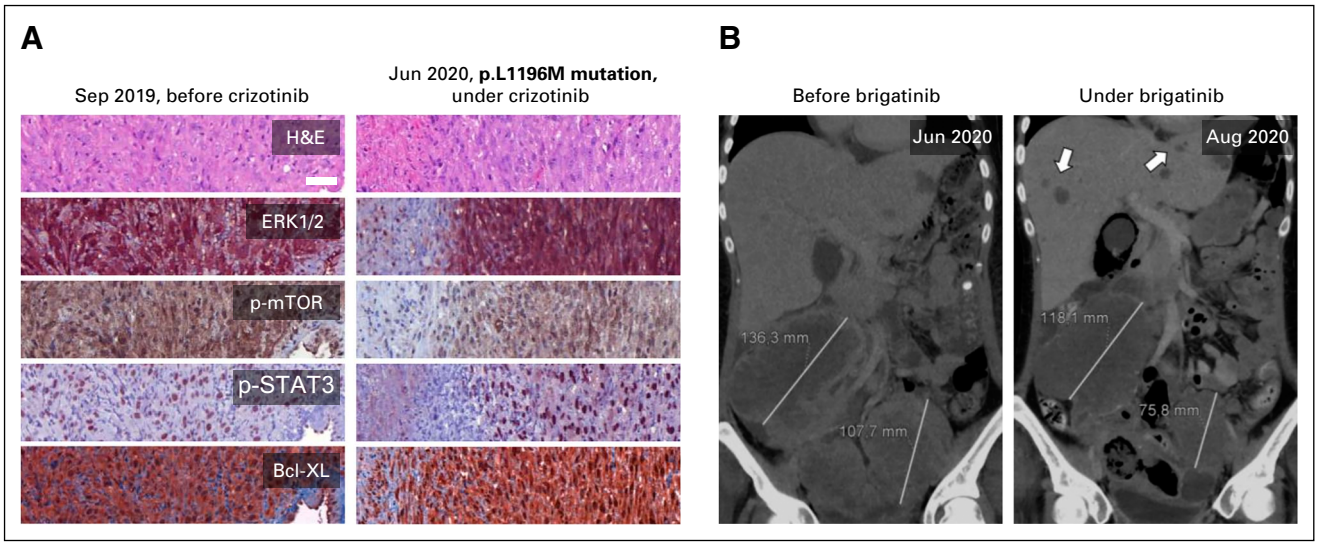

FIG 4. ALK resistance mutation and mixed response under brigatinib therapy: (A) canonical ALK downstream effectors are strongly activated in a precrizotinib biopsy (left panels) and a biopsy during crizotinib treatment harboring an ALK p.L1196M mutation (right panels) hinting at acquired resistance; scale bar = 50 μm; ERK1/2 (antibody #4370; Cell Signaling Technology, Cambridge, United Kingdom), p-mTOR (antibody #2976; Cell Signaling Technology), p-STAT3 (antibody #9145; Cell Signaling Technology), and Bcl-XL (antibody #2764; Cell Signaling Technology); and (B) coronal reformation of contrast-enhanced computed tomography scans before (left panel) and 2 months after initiation of brigatinib therapy (right panel), showing mixed response with a significant decrease of tumor diameters but new onset of liver metastases (white arrows). Bcl-XL, B-cell lymphoma-extra large; ERK1/2, extracellular signal–regulated kinases 1 and 2; H&E, hematoxylin and eosin; p-mTOR, phospho(Ser2448)-mammalian target of rapamycin; p-STAT3, phospho(Tyr705) signal transducer and activator of transcription 3.

characterized in MPM and subsequently treated with brigatinib. Several preclinical studies showed a possible response to ALK inhibitors like brigatinib, alectinib, and ceritinib.[13,23-26] In particular, brigatinib is a highly potent ALK inhibitor in the presence of *ALK* mutations such as L1196M with lower IC50 values than, for instance, ceritinib and alectinib.[27] The observed size reduction of the biopsied lesion harboring the p.L1196M *ALK* resistance mutation suggests the effectivity of brigatinib in this specific mutational context. However, since other lesions apparently progressed under brigatinib therapy, a significant tumoral heterogeneity with diverse resistance mechanisms might have precluded treatment success. In fact, it has been demonstrated for lung cancer before that several ALK resistance mechanisms can often be detected simultaneously by means of liquid biopsy,[28] which could have been of great benefit in the case presented here. An additional notable finding was the upregulation of BCL-xL, which was already observed before the initiation of crizotinib treatment. BCL-xL could potentially represent a mediator of primary crizotinib resistance here, and it could constitute an additional therapeutic target in the future.[29,30]

To our knowledge, this is the first description of an *STRN-ALK* fusion(+) MPM sequentially treated with two different ALK inhibitors. This case underlines the benefit of molecular testing in MPM. Furthermore, it suggests the generalizability of the lessons learned from lung cancer to another entity, which can offer some guidance in the treatment of this rare disease.

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DATA SHARING STATEMENT

Additional data are available on request.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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