case report

Durable Clinical Response to Larotrectinib in an Adolescent Patient With an Undifferentiated Sarcoma Harboring an *STRN-NTRK2* Fusion

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INTRODUCTION

Nonrhabdomyosarcoma soft tissue sarcomas (NRSTSs) are a heterogeneous group of tumors comprising approximately 4% of all pediatric cancers.[1-3] Histologic diagnosis of NRSTS is challenging, with frequent revisions of the diagnosis on central review.[4] Prognosis is largely determined by histologic grade, size, and stage, with the worse outcomes for patients with metastatic disease.[2,5] Many subtypes of NRSTS are characterized by different, but highly recurrent, gene fusions like *SS18-SSX* fusions in synovial sarcoma,[6] *TPM-ALK* fusions in inflammatory myofibroblastic tumors,[7,8] and *COL1A1-PDGFRB* fusions in dermatofibrosarcoma protuberans.[9] Irrespective of the genomic basis of these cancers, most patients are treated with surgery, radiation, and/or chemotherapy regimens including alkylators and/or anthracyclines.[10] Exceptions include the use of imatinib for dermatofibrosarcoma protuberans and crizotinib for ALK-rearranged inflammatory myofibroblastic tumors.[11,12] Undifferentiated sarcomas, a subset of NRSTSs, lack a clear line of differentiation after pathologic evaluation but may also harbor frequent oncogenic fusions.[13]

The neurotrophin tyrosine kinase receptors TRKA, TRKB, and TRKC are encoded by the *NTRK1*, *NTRK2*, and *NTRK3* genes, respectively. In normal development, these genes regulate the growth, differentiation, and survival of neurons.[14,15] Gene fusions that involve one of these genes (TRK fusions) have been described in a range of pediatric and adult cancers.[16-25] In these fusions, the 3′ region of the *NTRK* gene, which includes the kinase domain, is joined downstream of the promoter and 5′ region of an unrelated gene. The resultant fusion oncoprotein is both aberrantly expressed and constitutively active. Most reported fusions in extracranial solid tumors to date have involved either *NTRK1* or *NTRK3*, with *NTRK2* fusions more common in primary CNS tumors.[26]

Larotrectinib is the first highly selective inhibitor of all three TRK kinases to enter clinical development. Recently, a centrally confirmed 75% objective response rate to larotrectinib (80% by investigator assessment) has been reported in adults and children with TRK fusion-positive solid tumors.[27] We report the clinical activity of larotrectinib in the first patient with an *NTRK2* fusion.

CASE REPORT

An 11-year-old female presented with back and leg pain for 1 month. Computed tomography of her abdomen and pelvis revealed a large (9.6 × 7.4-cm), unresectable, retroperitoneal mass encasing the aorta and involving the vertebral bodies (Fig 1A). Biopsy led to the diagnosis of NRSTS, likely hemangiopericytoma, which upon review at our institution was revised to undifferentiated sarcoma. The patient underwent neoadjuvant chemotherapy of vincristine, cyclophosphamide, and doxorubicin followed by etoposide and ifosfamide. After two cycles of chemotherapy, disease progression continued, and an aortic pseudoaneurysm developed within the mass, which led to displacement of the inferior vena cava and ureteral impingement (Fig 1B). Hospice was recommended, and the patient was treated with palliative sorafenib, but tumor progression continued.

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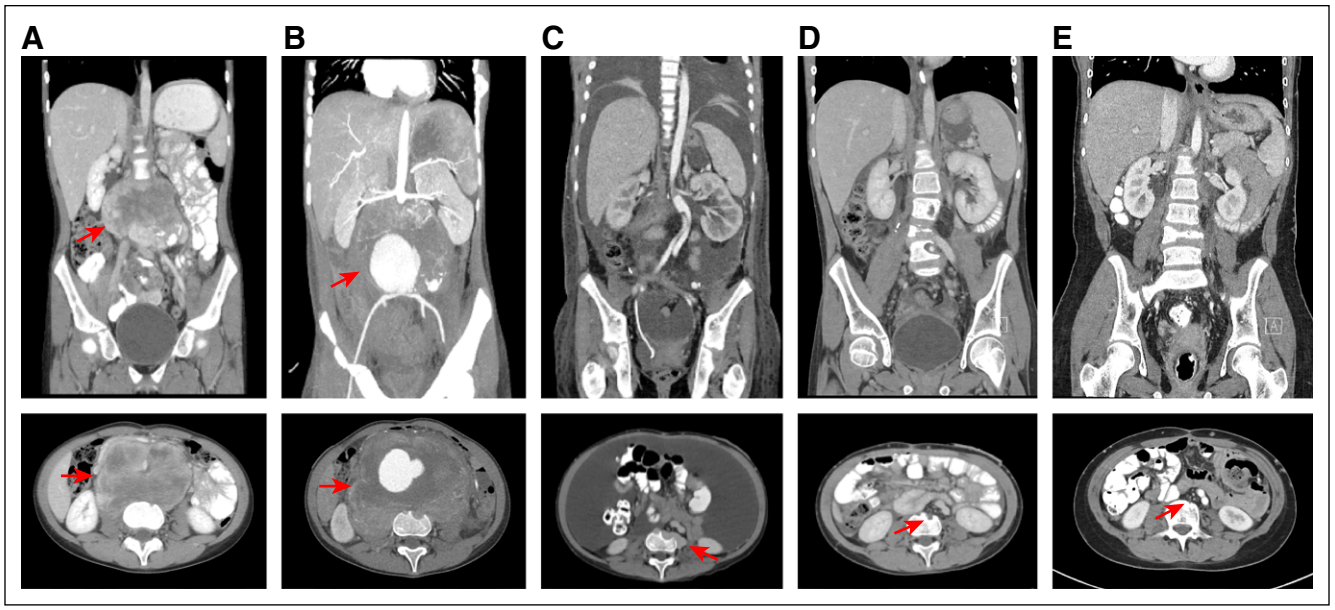

Fig 1. Computed tomography imaging of patient's abdominal tumor over time. (A) Initial imaging. (B) Development of aortic pseudo-aneurysm. (C) Baseline before enrollment, postsurgery. (D) After 1.6 months of larotrectinib treatment. (E) After 14 months of larotrectinib treatment.

The patient was subsequently referred to our institution, where surgical intervention to debulk the tumor and repair the pseudo-aneurysm was offered. She underwent exploratory laparotomy with resection of a 13.5 × 10.5 × 6.5-cm tumor, resection and reconstruction of the abdominal aorta, ligation and resection of the inferior vena cava, resection of sigmoid colon with end colostomy, and placement of bilateral ureteral stents (Fig 2). Histologically, the tumor consisted of sheets of epithelioid cells with large eccentrically placed nucleus, occasional nucleoli, and abundant eosinophilic cytoplasm, mimicking rhabdoid cells (Fig 3). Immunohistochemically, the cells showed retained INI-1 nuclear positivity and scattered cells positive for S-100 protein and CD34.

Postoperatively, gross residual tumor remained in the vertebral bodies. Subsequently, the patient developed prolonged ileus, anasarca, and symptomatic ascites that required Denver venous shunt placement. After a prolonged recovery, she was treated with irinotecan. Next generation sequencing (NGS) of her tumor was performed using FoundationOneHeme (Foundation Medicine, Cambridge, MA), a combined DNA and RNA sequencing hybrid capture-based assay that has been validated for clinical use without requirement for an orthogonal confirmatory assay.[28] Sequencing revealed a novel *STRN-NTRK2* fusion in which the kinase domain of *NTRK2* is joined in frame to *STRN* (Figs 3E and 3F). Copy number loss of *CDKN2B* also was identified.

Two months after surgery, after informed consent, the patient was enrolled in the pediatric phase I trial of larotrectinib.[29] She was treated with dose level 1 (100-mg adult equivalent dose by Simcyp modeling [Simcyp, Sheffield, UK]) and received larotrectinib 75 mg twice a day continuously on the basis of her age and body surface area. Pharmacokinetic assessment after the first dose of larotrectinib revealed an estimated 24-hour area under the plasma concentration-time curve ($AUC_{0\text{-}24}$) of 2,980 ng · h/mL, which was less than the protocol-specified threshold of 3,500 ng · h/mL that would allow intrapatient dose escalation. Thus, per protocol, the patient's dose was increased to 100 mg twice a day on day 10 of cycle 1. Pharmacokinetics at this dose demonstrated an estimated $AUC_{0\text{-}24}$ of 3,830 ng · h/mL.

At the time of initiation of larotrectinib, the patient's Lansky play-performance score (LPS) was 60. She had a distended firm abdomen with significant ascites and back pain that required daily narcotic pain medication. Baseline disease evaluation revealed the presence of a pulmonary metastasis, multiple enlarging positron emission tomography (PET)–avid tumors (largest 1.5 × 5.3 cm) within the retroperitoneal surgical bed, and massive ascites that was presumed to be malignant (Fig 1C). By 14 days after initiation of larotrectinib, the patient was noticeably less fatigued (LPS of 70), the ascites had resolved by physical examination, and her back pain had resolved (Fig 4). Repeat imaging at the end of cycle 1, which was confirmed after cycle

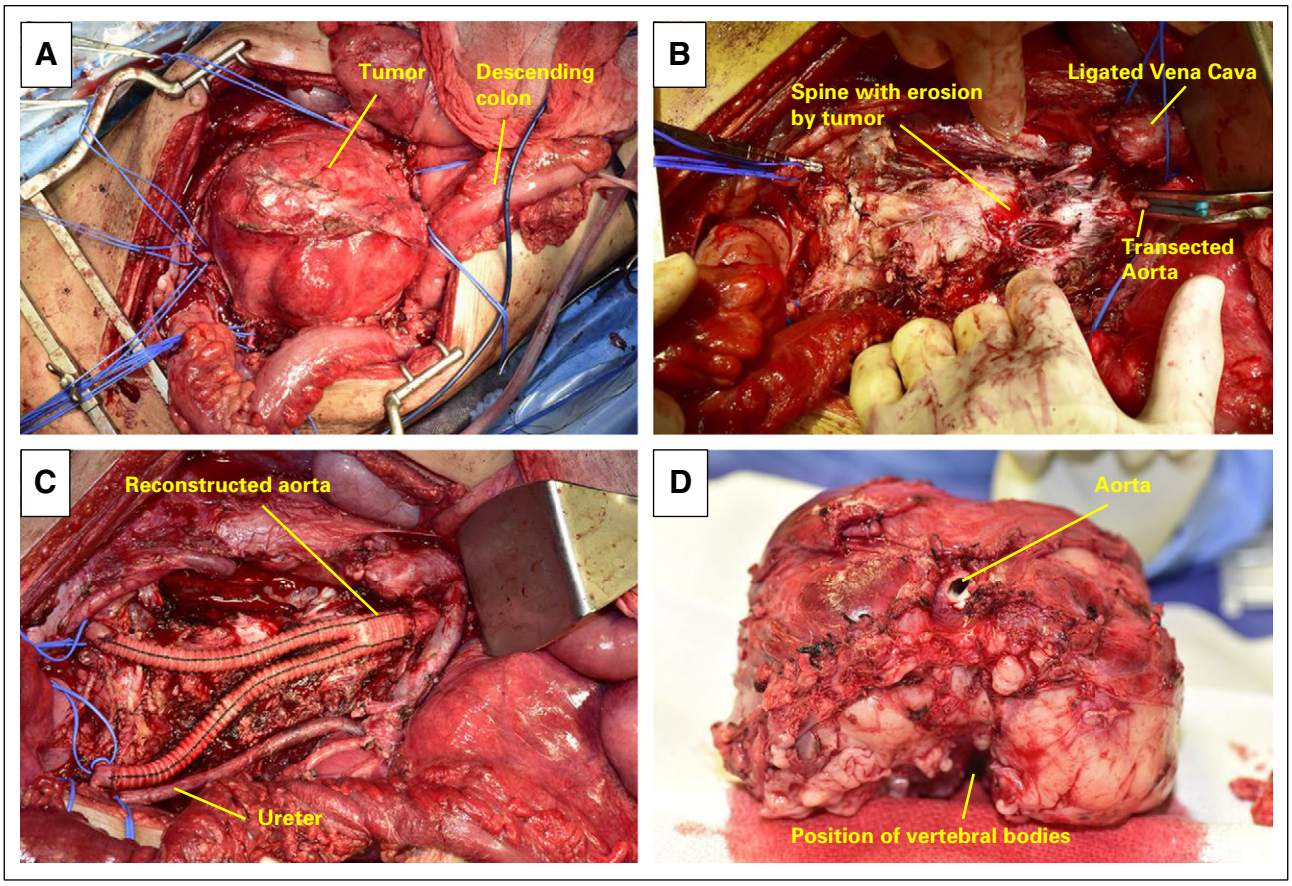

Fig 2. Surgical resection of retroperitoneal sarcoma. (A) Retroperitoneal tumor before resection. (B) Tumor bed after resection, with residual tumor invading the vertebral bodies. (C) Status postreconstruction of the aorta. (D) Excised tumor specimen, including the aortic bifurcation.

2, demonstrated resolution of PET avidity of all tumors, resolution of ascites, and significant reduction in the size of the residual pulmonary metastases and retroperitoneal tumors consistent with a partial response by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (Figs 1D and 1E). Five months after starting larotrectinib, the patient underwent uncomplicated closure of her colostomy and removal of her Denver shunt.

Despite heavy pretreatment, the patient has tolerated larotrectinib well, with the only drug-related adverse events consisting of mild (Common Terminology Criteria for Adverse Events [version 4] grade 1) fatigue and intermittent grade 1 to 2 cytopenias. She has not required dose reduction or interruption for toxicity. Her response continues to deepen with complete resolution of her pulmonary metastasis and only residual PET-negative tissue at the site of tumor invasion of the vertebral bodies after 22 months of larotrectinib therapy as of February 2018. Currently, the patient's LPS is 90, and she has returned to school.

DISCUSSION

We describe a patient in whom tumor sequencing led to the identification of a novel *NTRK2* fusion in a chemotherapy-refractory, metastatic, unresectable, undifferentiated sarcoma and successful treatment with larotrectinib. The identification of an *NTRK2* fusion is consistent with other reports of oncogenic fusions in this histology.[13,30-39] A wide range of tumors that harbor TRK fusions has been reported to respond to larotrectinib.[27] The activity of larotrectinib is striking in children, with a 93% confirmed objective response rate and all patients with TRK fusions experiencing tumor regression.[29]

This patient's tumor harbored a fusion of *NTRK2*, and she was the sole patient in the initial 55-patient data set to have a fusion of this gene.[27] Other rare *NTRK2* fusions have been described in gliomas, specifically with *VCL*, *AGBL4*, *QKI*, and *NACC2*,[20,40] but to our knowledge, this report is the first of an *NTRK2* fusion in a pediatric extracranial solid tumor. The morphologic similarity of the patient's tumor to soft tissue sarcomas that harbor fusions of *NTRK1* and

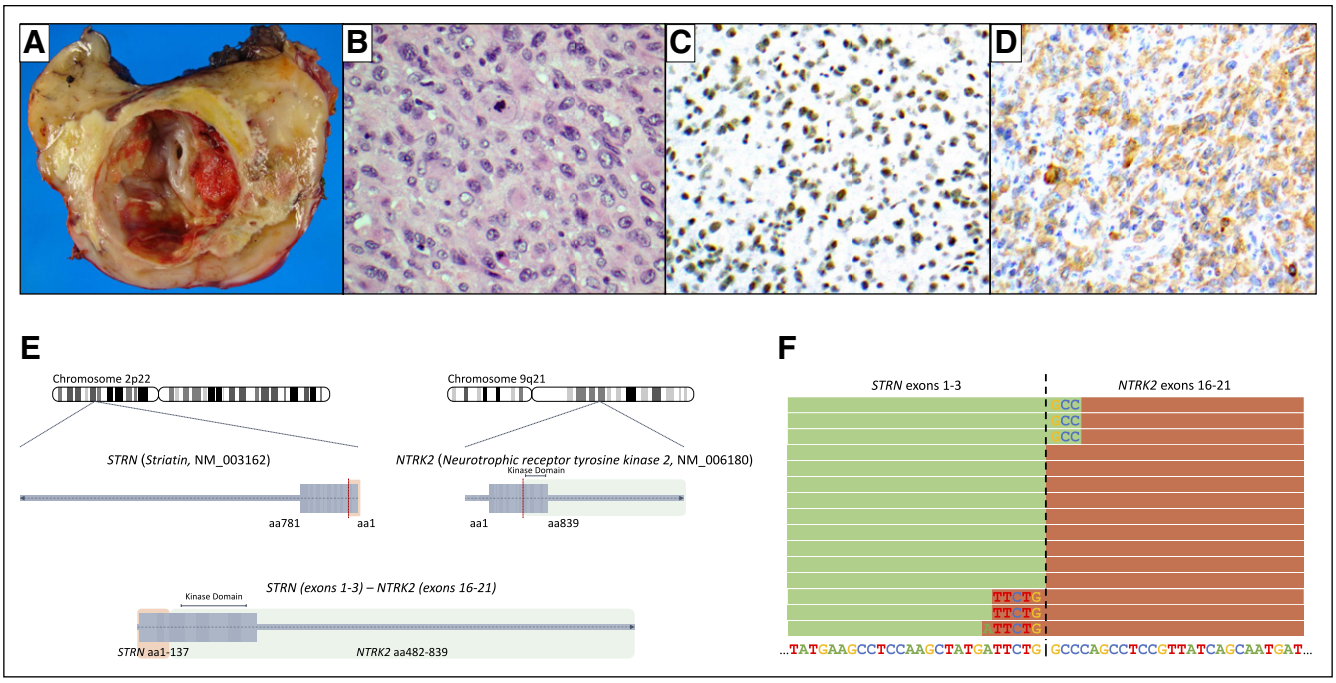

Fig 3. Pathology of patient's tumor from resection. (A) Transverse section of the mass with aneurysmal cavity around the aorta. (B) Hematoxylin and eosin stain that shows epithelioid/rhabdoid cells with eccentric, pleomorphic nuclei; occasional nucleoli and abundant eosinophilic cytoplasm; and a single mitosis. (C) Immunohistochemistry for INI-1 that shows retained nuclear positivity in the neoplastic cells. (D) Immunohistochemistry for pan-Trk that shows membranous and cytoplasmic positivity in the neoplastic cells. (E) *STRN-NTRK2* fusion identified in tumor sample by next generation sequencing. (F) RNA sequencing reads that support the *STRN-NTRK2* fusion.

NTRK3 suggests that these sarcomas should be evaluated for fusions of all three NTRK genes.[41]

STRN on chromosome 2p22.2 encodes striatin, a ubiquitously expressed calmodulin-binding protein. In thyroid cancer, it is a common 5′ fusion partner for *ALK* also located on 2p.[42] However, *STRN* has not previously been reported as an NTRK fusion partner, which is consistent with the broad diversity of 5′ fusion partners seen in TRK fusion-positive cancers[27] and is an important consideration when designing testing strategies for TRK fusions. Tests such as reverse transcriptase polymerase chain reaction only detect known fusion partners and are likely to miss tumors with uncommon or unique NTRK fusion genes, which can respond to TRK inhibition. Testing that uses hybrid capture–based NGS has the potential to detect a diversity of NTRK fusion partners, but careful attention must be paid to the initial substrate (DNA *v* RNA), the target enrichment strategy (hybrid capture *v* amplicon *v* anchored multiplex polymerase chain reaction), and the detailed probe design.

The profound clinical response seen in this *STRN-NTRK2* fusion patient to larotrectinib establishes that the TRK fusion is the key driver for this patient's tumor. Her duration of response (ongoing at 22 months) compares favorably with that seen with other tyrosine kinase inhibitors, such as BRAF inhibitors for $BRAF^{V600E}$ mutant melanoma. In the latter, despite high initial response rates, nearly all patients treated with vemurafenib or dabrafenib experience disease progression within 12 to 18 months of starting therapy.[43,44] Durable responses also have been observed in patients with fusions that involve *NTRK1* and *NTRK3* treated with larotrectinib.[27]

In conclusion, NGS of the undifferentiated sarcoma in our patient was critical in identifying a highly actionable kinase fusion (*STRN-NTRK2*), which resulted in a profound and durable clinical response on matched treatment. Genomic and molecular testing of tumors have become increasingly useful for treatment through the identification of potential targets for novel therapies irrespective of histology. Such testing should be considered for all patients with advanced cancer, especially those with NRSTS, because both classic and novel fusion oncogenes can be detected without a prior therapeutic hypothesis.

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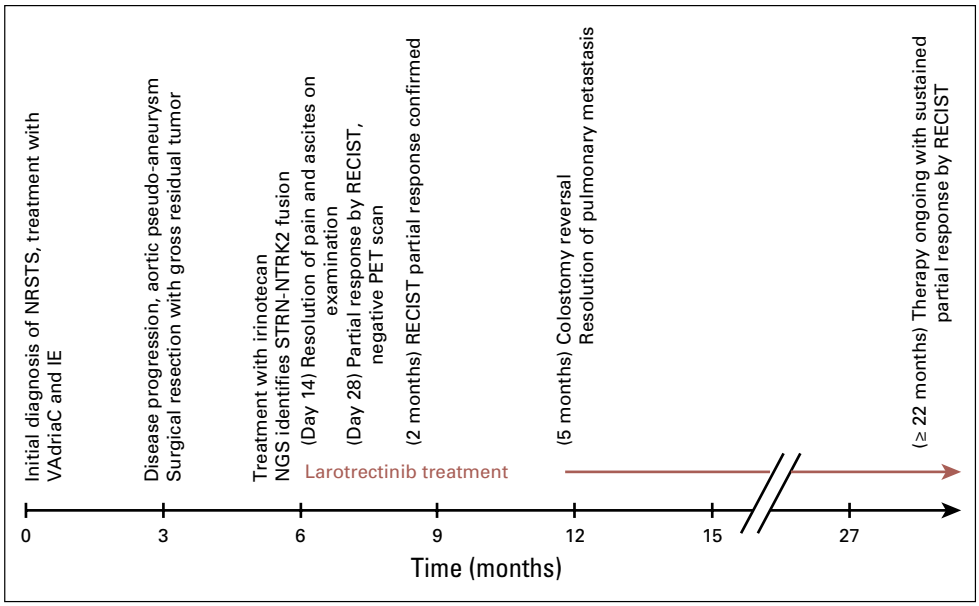

Fig 4. Timeline. IE, ifosfamide and etoposide; NGS, next-generation sequencing; NRSTS, nonrhabdomyosarcoma soft tissue sarcoma; PET, positron emission tomography; RECIST, Response Evaluation Criteria in Solid Tumors; VAdriaC, vincristine, doxorubicin, and cyclophosphamide.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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