

Rare FGFR Oncogenic Alterations in Sequenced Pediatric Solid and Brain Tumors Suggest FGFR Is a Relevant Molecular Target in Childhood Cancer

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PURPOSE Multiple FGFR inhibitors are currently in clinical trials enrolling adults with different solid tumors, while very few enroll pediatric patients. We determined the types and frequency of *FGFR* alterations (*FGFR1-4*) in pediatric cancers to inform future clinical trial design.

METHODS Tumors with *FGFR* alterations were identified from two large cohorts of pediatric solid tumors subjected to targeted DNA sequencing: The Dana-Farber/Boston Children's Profile Study (n = 888) and the multi-institution GAIN/iCAT2 (Genomic Assessment Improves Novel Therapy) Study (n = 571). Data from the combined patient population of 1,395 cases (64 patients were enrolled in both studies) were reviewed and cases in which an *FGFR* alteration was identified by OncoPanel sequencing were further assessed.

RESULTS We identified 41 patients with tumors harboring an oncogenic *FGFR* alteration. Median age at diagnosis was 8 years (range, 6 months-26 years). Diagnoses included 11 rhabdomyosarcomas, nine low-grade gliomas, and 17 other tumor types. Alterations included gain-of-function sequence variants (n = 19), amplifications (n = 10), oncogenic fusions (*FGFR3::TACC3* [n = 3], *FGFR1::TACC1* [n = 1], *FGFR1::EBF2* [n = 1], *FGFR1::CLIP2* [n = 1], and *FGFR2::CTNNA3* [n = 1]), pathogenic-leaning variants of uncertain significance (n = 4), and amplification in combination with a pathogenic-leaning variant of uncertain significance (n = 1). Two novel *FGFR1* fusions in two different patients were identified in this cohort, one of whom showed a response to an FGFR inhibitor.

CONCLUSION In summary, activating *FGFR* alterations were found in approximately 3% (41/1,395) of pediatric solid tumors, identifying a population of children with cancer who may be eligible and good candidates for trials evaluating FGFR-targeted therapy. Importantly, the genomic and clinical data from this study can help inform drug development in accordance with the Research to Accelerate Cures and Equity for Children Act.

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ASSOCIATED CONTENT

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Oncogenic *FGFR1-4* alterations occur at different frequencies in multiple types of solid tumors including head and neck cancer, lung cancer, breast cancer, and cholangiocarcinoma.¹⁻⁶ *FGFR1-4* oncogenic mutations, fusions, and amplifications can activate the downstream MAPK-ERK, PI3K/AKT, and/or JAK-STAT pathway.⁷⁻¹⁰ Pediatric cancers such as rhabdomyosarcoma (RMS) harbor recurrent *FGFR4* sequence variants and low-grade gliomas (LGG) harbor recurrent *FGFR1/2* variants and fusions, including intragenic duplications in *FGFR1* affecting the tyrosine kinase domain.¹¹⁻¹³

FGFR-tyrosine kinase inhibitors (TKIs) are under clinical investigation, with early trials reporting response rates up to 20%-40% primarily in patients with well-characterized *FGFR*-activating alterations.¹⁴⁻¹⁶ These include specific FGFR4 inhibitors and pan-FGFR inhibitors (FGFR1-3 and FGFR1-4).¹⁴⁻¹⁶ Pemigatinib, infigratinib, and erdafitinib, three highly selective US Food and Drug Administration (FDA)-approved pan-FGFR inhibitors, have defined on-target toxicities including hyperphosphatemia, vision changes, and skin and nail changes.¹⁴ To decrease toxicity and address the development of resistance variants in *FGFR1-4*, additional compounds are under clinical investigation

CONTEXT

Key Objective

FGFR alterations occur in multiple adult cancers and have previously been found in some pediatric tumors including rhabdomyosarcoma and low-grade glioma. To better define the relevance of *FGFR* as a molecular target in children with cancer, this study identified and characterized *FGFR*-activating alterations in a large cohort of sequenced pediatric cancers.

Knowledge Generated

Activating *FGFR1-4* alterations were identified in 3% of pediatric solid tumors across 19 different histologies, thus highlighting a population of patients that may benefit from pediatric trials of *FGFR*-targeted therapies. The study also provides proof-of-concept evidence of clinical efficacy in an infant with a spindle-cell sarcoma with a novel *FGFR1* fusion treated with erdafitinib.

Relevance

Although many *FGFR*-targeting compounds are under development for adults, the availability of these drugs for children with cancer is quite limited. The findings from this study significantly inform pediatric drug development in accordance with the Research to Accelerate Cures and Equity for Children Act.

including derazantinib, rogaratinib, and futibatinib.¹⁴ A recent trial of futibatinib (TAS-120), the only irreversible pan-*FGFR* inhibitor, showed an objective response rate of 13.7% and notably included patients with previously uncharacterized *FGFR1-3* alterations.¹⁷ Importantly, futibatinib can overcome resistance to reversible ATP-competitive *FGFR* inhibitors including infigratinib.^{17,18}

Despite the numerous compounds under development targeting *FGFR*, the number of clinical trials and the availability of these drugs to children with different cancers are quite low. The Research to Accelerate Cures and Equity (RACE) for Children Act was enacted to remove clinical indication and orphan drug designation–based waivers that previously limited requirements for pediatric cancer drug development. This law authorizes the FDA to mandate pediatric studies of molecular targeted therapies if the target is relevant to the growth or progression of one or more pediatric cancers.¹⁹ Here, we aimed to determine the frequency and types of *FGFR1-4* variants in pediatric solid tumors and the diagnoses in which they occur to better define the relevance of *FGFR* as a molecular target in pediatric cancer and facilitate the design of clinical trials of *FGFR* inhibitors in children.²⁰ We integrated genomic data from two cohorts of patients with pediatric CNS and extracranial solid tumors subjected to targeted DNA sequencing to identify pediatric patients with oncogenic *FGFR* alterations and describe the genomic alterations and clinical features of these pediatric *FGFR*-altered malignancies.

METHODS

Patients and Samples

This study was approved by the Dana-Farber Cancer Institute (DFCI, Boston, MA) Institutional Review Board with a waiver of informed consent. The study included patients from two sequencing studies who had tumor samples

sequenced with OncoPanel, a targeted DNA next-generation sequencing panel, between January 1, 2013, and July 1, 2021. The GAIN Consortium study (ClinicalTrials.gov identifier: [NCT02520713](https://clinicaltrials.gov/ct2/show/study/NCT02520713)) is a prospective cohort study enrolling patients age ≤ 30 years with relapsed/refractory and high-risk pediatric extracranial solid tumors at 12 institutions to determine the clinical impact of molecular tumor profiling.²¹ The Dana-Farber/Boston Children's Profile Cancer Research Study, offered to all pediatric oncology patients with a variety of solid malignancies and lymphomas since 2013, facilitates research on cancer biology and informs ongoing and potential trials assessing targeted therapies. Patients enrolled on either study were included in this analysis if they had at least one successful targeted DNA sequencing result and a CNS or extracranial solid malignancy. Patients with lymphoma were excluded.

Patient Clinical Information

Medical records were reviewed to obtain demographic, clinical, and specimen variables including cancer diagnosis, age at diagnosis, sex, stage at diagnosis, tumor biopsy site, timing of tumor acquisition, and treatments. Timing of tumor acquisition was defined as at initial diagnosis (which included local control surgery during upfront treatment) or at relapse/progression. Sequencing data for all eligible patients were obtained from each study and used to identify patients with *FGFR1-4* genomic alterations (single-nucleotide variants [SNVs], amplifications, or fusions) on OncoPanel sequencing.

Molecular Tumor Profiling

Patients had at least one tumor sample (fresh frozen or archival formalin-fixed, paraffin-embedded tissue) sequenced using OncoPanel (Data Supplement). OncoPanel analysis includes the detection of SNVs, insertions and deletions (indels), copy-number (CN) alterations, structural

variants (SV), tumor mutational burden, and microsatellite instability, as previously described.²²⁻²⁴ *FGFR2* introns are not covered for fusion detection by OncoPanelV1 (7% of cohort was tested with this version), and *FGFR4* introns are not covered for fusion detection by any version as *FGFR4* fusions are rarely reported in cancer. CN estimates for amplifications (defined as $CN \geq 7$) were only available for tumors sequenced with OncoPanelV3. Of note, OncoPanel is not optimized to identify intragenic *FGFR* duplications but does detect extracellular in-frame deletions.²⁵ A molecular pathology report was returned to treating providers at the time of sequencing, and data were made available for this analysis in August 2021.

Variant Interpretation

Variant curation was conducted using multiple databases, primary literature, and other criteria as detailed in the Data Supplement. The following were considered activating alterations of *FGFR1-4*: amplifications ($CN \geq 7$) on the basis of the adult NCI-MATCH eligibility criteria for *FGFR* amplifications (ClinicalTrials.gov identifier: [NCT02465060](https://clinicaltrials.gov/ct2/show/study/NCT02465060)); in-frame oncogenic fusions with an intact protein tyrosine kinase domain (TKD); pathogenic SNVs and indels; and pathogenic-leaning variants of uncertain significance (PL-VUS). Other *FGFR* variants of uncertain significance (VUS) were identified and excluded from further assessment.

Clinical Trial Data Access

We identified clinical trials evaluating *FGFR* inhibitors using ClinicalTrials.gov. We collected recruitment status, phase, and age of eligibility for clinical trials of six *FGFR* inhibitors being investigated in the United States—derazantinib, rogaratinib, futibatinib, pemigatinib, infigratinib, and erdafitinib—as of January 20, 2022.

RESULTS

FGFR1-4 Activating Alteration Frequency and Case Characteristics

The study population included 888 patients enrolled on the Profile Cancer Research Study and 571 patients enrolled on the GAIN Consortium Study for a total of 1,395 patients (64 patients enrolled on both) with 93% sequenced on OncoPanel versions 2 or 3 (Data Supplement). Forty-one patients (3%) had tumors with activating *FGFR1-4* alterations (Fig 1). Twenty-six patients (63%) were male. Median age at diagnosis was 8 years (range, 6 months-26 years; Data Supplement). Four disease groups were represented (sarcomas [$n = 18$], CNS tumors [$n = 15$], carcinomas [$n = 4$], other embryonal tumors [$n = 4$]; Table 1 and Data Supplement). Across these groups, there were 19 distinct diagnoses (Data Supplement). The most common diagnoses were RMS ($n = 11$) and LGG ($n = 9$), which together comprised 49% of the cohort. Other diagnosis included Ewing sarcoma, glioblastoma, osteosarcoma, and Wilms tumor. Of the 11 RMS, eight were fusion-negative and three were *PAX3::FOXO1* fusion-positive (Fig 1). Sequenced

samples were from the primary site at initial diagnosis for 68% of patients. One patient with a tumor harboring an activating *FGFR* alteration was treated with an *FGFR* inhibitor. An additional 95 patients had tumors with an *FGFR* VUS that were not considered activating (Data Supplement).

Activating FGFR Alterations Identified

Pathogenic *FGFR1-4* SNVs, identified in 19 tumors (46%), were the most frequent type of alteration in this cohort. Eleven tumors (27%) had an amplification (CN range, 7-30) and seven (17%) had a fusion. Four tumors (10%) had a PL-VUS, one of which also had an amplification. Activating alterations occurred most often in *FGFR1* ($n = 21$) followed by *FGFR4* ($n = 11$). Two tumors from the primary site harbored two activating *FGFR1* alterations at initial diagnosis including a RMS (amplification [$CN = 30$], PL-VUS) and LGG (p.N546K; p.K656N; Fig 1). Tumors from patients with RMS harbored recurrent *FGFR4* missense variants (5/11), *FGFR1* amplifications (3/11), and *FGFR4* amplifications (3/11; all in fusion-positive RMS). LGGs harbored *FGFR1* variants (5/9) and *FGFR1-3* fusions (4/9). The sarcomas harbored *FGFR1* amplifications (4/7), *FGFR1* fusion (1/7), and *FGFR2/4* SNVs (2/7), while *FGFR1* SNVs and *FGFR3* alterations were found across other disease groups (Data Supplement). Extracellular *FGFR2* in-frame deletions recently reported in cholangiocarcinoma (also via OncoPanel sequencing) were not seen in this cohort.²⁵

Tumors with an *FGFR* missense variant were primarily those with an oncogenic hotspot variant in *FGFR1* (N546K [$n = 5$]; K656E [$n = 4$]) and *FGFR4* (N535K/D [$n = 2$]; V550L/E [$n = 5$]). Of note, 21 of 41 (51%) of the tumors had at least one *FGFR* missense variant located in the TKD (Fig 2A). The *FGFR4* V550L/E gatekeeper mutation known to induce TKI resistance was identified in four of five patients with RMS, consistent with previous studies reporting this variant in embryonal RMS.²⁶

FGFR fusions with an intact TKD accounted for 17% (7/41) of the activating *FGFR* alterations. An *FGFR3::TACC3* fusion was identified in two carcinomas and one LGG. We also identified two previously reported fusions in LGGs including an *FGFR1::TACC1* fusion and an *FGFR2::CTNNA3* fusion.^{12,27} Two novel fusions were identified: *FGFR1::CLIP2* fusion in a patient with LGG and *FGFR1::EBF2* fusion in a patient with a spindle-cell sarcoma (Fig 2B).

Amplifications accounted for 27% (11/41) of the *FGFR* alterations (Data Supplement). Seven tumors harbored *FGFR1* amplifications, four of which were further evaluated for *FGFR1* gene expression using RNA sequencing and showed high expression levels (Data Supplement). One tumor harbored an *FGFR3* amplification ($CN = 7$). Three tumors from patients with fusion-positive RMS harbored focal *FGFR4* amplifications: one had an estimated $CN = 7$, and two had a high-level amplification ($CN > 7$; Fig 1).

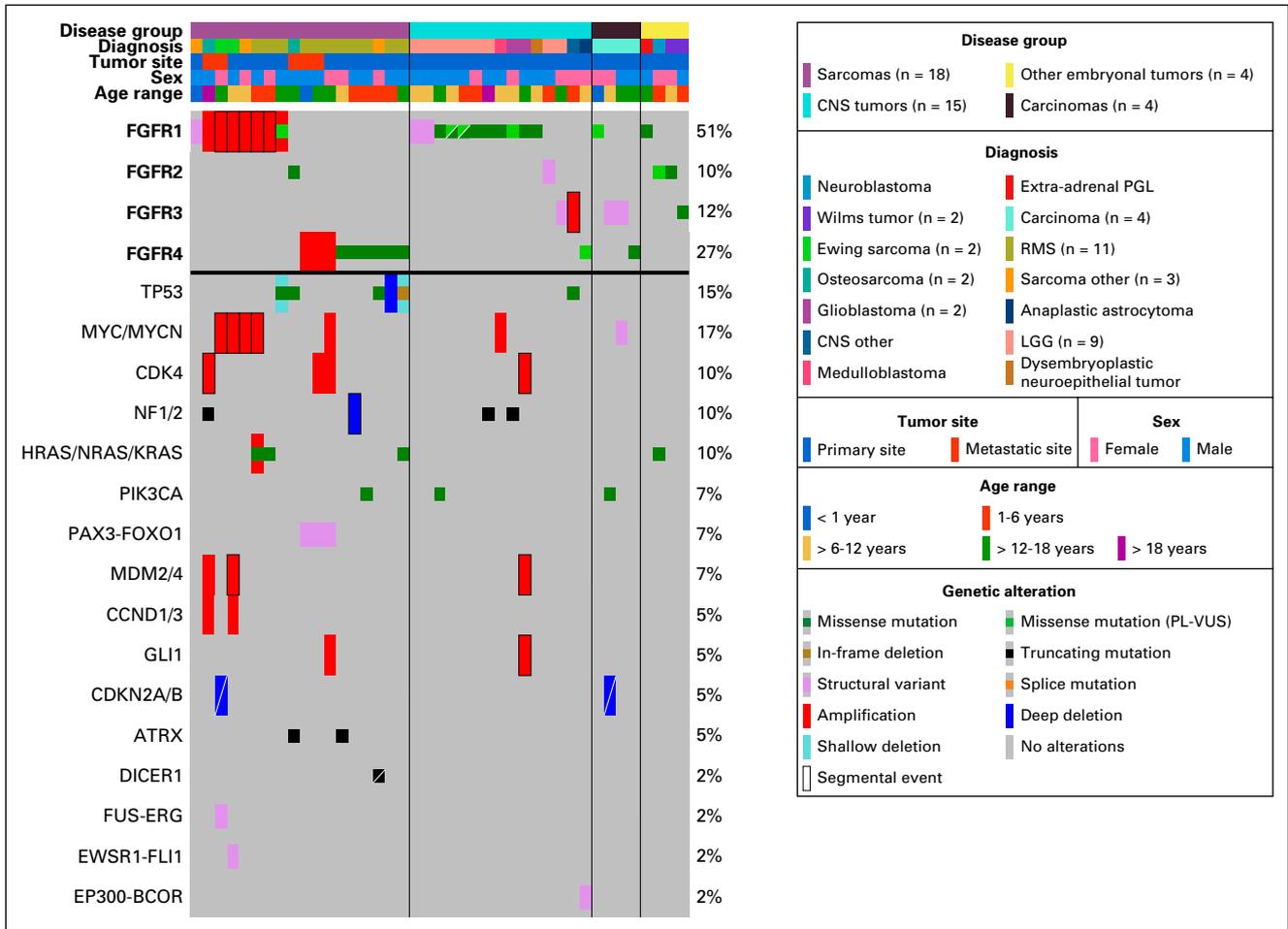


FIG 1. Genomic and clinical features of 41 pediatric patients with at least one activating *FGFR* alteration. OncoPrint shows clinical features including disease group, diagnosis, tumor site, sex, and age at diagnosis as well as oncogenic or likely oncogenic variants in genes altered in more than one patient or alterations with diagnostic implications. LGG, low-grade glioma; PGL, paraganglioma; PL-VUS, pathogenic-leaning variants of uncertain significance; RMS, rhabdomyosarcoma

Molecular Landscape of Pediatric Cancers Harboring *FGFR* Alterations

Co-occurring oncogenic alterations were commonly seen in the 41 tumors with activating *FGFR* alterations. *MYC/MYCN* amplification was the most recurrent alteration along with *TP53*-inactivating alterations identified in 17% and 15% of the *FGFR*-altered tumors, respectively. Of interest, the RAS pathway was activated through *HRAS/NRAS/KRAS* alterations, including a *KRAS* G12V variant, or *NF1/2* inactivating alterations in 17% (7/41) of the *FGFR*-altered tumors. Activation of oncogenes (*PIK3CA* and *MDM2/4*), inactivation of tumor suppressors (*ATRX*), and cell cycle dysregulation (*CDK4*, *CDKN2A/B*, and *CCND1/3*) were also seen (Fig 1 and Data Supplement).

Additional alterations with diagnostic implications included three *PAX3::FOXO1* fusions in RMS, a *EWSR1::FLI1* fusion in a Ewing sarcoma, a *EP300::BCOR* fusion in a CNS tumor, and a *DICER1*-truncating alteration in a *DICER1*-associated sarcoma (Fig 1 and Data Supplement).

Eligibility for Clinical Trials

Review of clinical trials actively recruiting patients with *FGFR* alterations in ClinicalTrials.gov identified 36 clinical trials assessing six *FGFR* inhibitors. Children age < 18 years were only eligible for two phase II studies assessing efficacy of erdafitinib (Data Supplement). Many patients in this cohort would have been eligible for the NCI/COG Pediatric MATCH treatment trial (ClinicalTrials.gov identifier: [NCT03210714](https://clinicaltrials.gov/ct2/show/study/NCT03210714)) assessing erdafitinib since 39% of the patients (16/41) with eligible fusions and SNVs were between age 1 and 21 years at the time of sample acquisition. Three patients between age 1 and 4 years likely would not have been eligible for the Pediatric MATCH trial because of inability to swallow pills. The Janssen Research & Development clinical trial (ClinicalTrials.gov identifier: [NCT04083976](https://clinicaltrials.gov/ct2/show/study/NCT04083976)) assessing erdafitinib includes patients age \geq 6 years. Nine patients (22%) were age \geq 6 years at sample acquisition and harbored eligible *FGFR* variants and fusions (Data Supplement).

TABLE 1. Summary of Clinical Information for Patients With an Activating *FGFR* Alteration

Characteristics	<i>FGFR1</i> (n = 21)	<i>FGFR2</i> (n = 4)	<i>FGFR3</i> (n = 5)	<i>FGFR4</i> (n = 11)	Total (N = 41), No. (%)
Cohort					
Gain	9	2	0	5	16 (39)
Profile	12	2	5	6	25 (61)
Sex					
Male	15	2	2	7	26 (63)
Female	6	2	3	4	15 (37)
Age range, years					
< 1	2	0	0	1	3 (7)
1-6	4	2	2	4	12 (29)
> 6-12	8	1	1	2	12 (29)
> 12-18	5	1	2	4	12 (29)
> 18	2	0	0	0	2 (5)
Disease group					
Sarcomas	8	1	0	9	18 (44)
Missense	0	1	0	6	7 (17)
Amp	7	0	0	3	10 (24)
SV	1	0	0	0	1 (2)
CNS tumors	11	1	2	1	15 (37)
Missense	9	0	0	1	10 (24)
Amp	0	0	1	0	1 (2)
SV	2	1	1	0	4 (10)
Carcinomas	1	0	2	1	4 (10)
Missense	1	0	0	1	2 (5)
SV	0	0	2	0	2 (5)
Other embryonal tumors	1	2	1	0	4 (10)
Missense	1	2	1	0	4 (10)

Abbreviations: Amp, amplification; SV, structural variant.

Overall, 20 patients (48% of those with *FGFR*-activating alterations) would not qualify for either trial because of the lack of eligible *FGFR* alterations including *FGFR* amplifications (n = 11), *FGFR4* gatekeeper variant (n = 5), and PL-VUS missense variants (n = 4). Additionally, three patients with Janssen-eligible alterations did not meet the age cutoff at diagnosis: two with fusions and one with an *FGFR3* R669Q SNV.

Pediatric Patient in the Cohort With Response to an FGFR Inhibitor

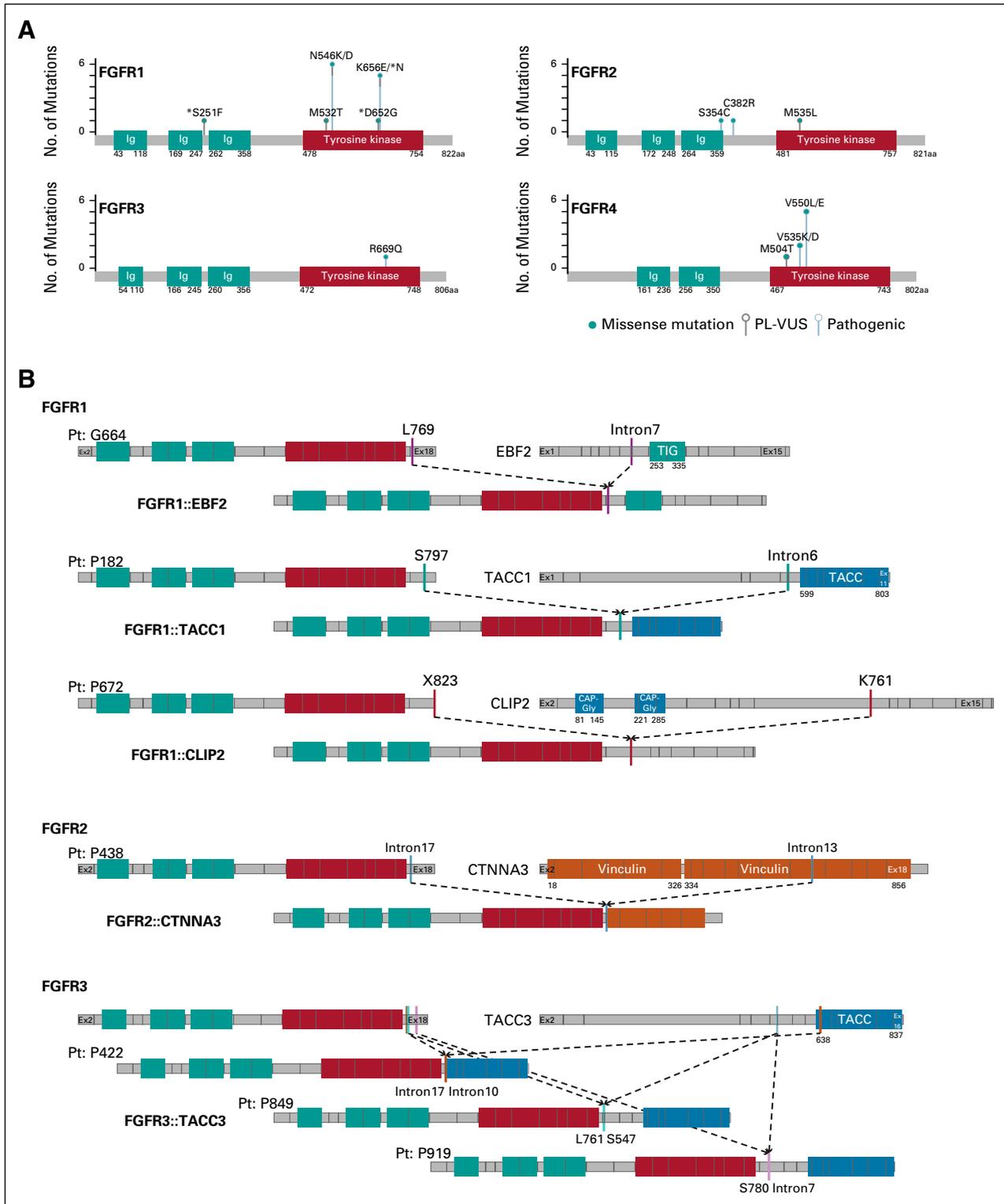
A previously healthy 9-month-old infant with a right thigh mass was the only patient with an *FGFR*-altered tumor who received targeted therapy with an FGFR inhibitor. Magnetic resonance imaging showed a large retroperitoneal heterogenous mass extending into the proximal right thigh. The predominantly T2 hypointense pelvic component measured 6.4 × 5.6 × 7.7 cm. The predominantly T2 hyperintense

thigh component measured 4.1 × 3.5 × 7.5 cm. Both components were biopsied given differences in imaging characteristics. Pathology revealed a spindle and round cell neoplasm (Fig 3A). Clinical testing for germline cancer predisposition (156 gene panel) revealed no pathogenic variants. OncoPanel sequencing revealed an oncogenic *FGFR1::EBF2* fusion.

Lenvatinib, a multitargeted TKI, was selected as the initial therapy as dosing and administration had been studied in children age as young as 2 years in Children’s Oncology Group (COG) protocol ADVL1711 (ClinicalTrials.gov identifier: NCT03245151).²⁸ During cycle 1, he developed toxicities including nausea, vomiting, thrombocytopenia, and hypothyroidism requiring hormone replacement and hypertension, leading to a dose reduction of lenvatinib. Imaging after eight weeks of lenvatinib therapy showed progression. Lenvatinib was stopped, and therapy was initiated with vincristine and actinomycin on the basis of COG infantile fibrosarcoma protocol ARST03P1 (ClinicalTrials.gov identifier: NCT00072280). After two cycles, imaging showed progression of the thigh mass, and cyclophosphamide was added in accordance with the infantile fibrosarcoma protocol. Vincristine was omitted from subsequent cycles because of toxicities (grade 3 cranial nerve neuropathy causing aspiration of liquids and necessitating placement of a gastrostomy tube). He received five additional cycles of actinomycin and cyclophosphamide with stable disease on imaging. Given the lack of objective response after the first two cycles, the treating team worked to identify an FGFR inhibitor with pediatric dosing and administration data. Surgery was consulted and resection was felt to be high risk for morbidity, given the extensive nature of the tumor. After seven cycles of chemotherapy, insurance approval was obtained for erdafitinib, which has pediatric toxicity data and guidelines for administration as a suspension. Three weeks before planned resection, erdafitinib was started at a dose of 4.7 mg/m² by G-tube once daily continuously. Cycle 1 of erdafitinib was complicated by hyperphosphatemia requiring a dose interruption, initiation of sevelamer, and a low-phosphorus diet. Physical examination after 5 days of erdafitinib was remarkable for a softer and smaller anterior thigh mass. After 12 weeks of erdafitinib (with two 7-day interruptions for hyperphosphatemia), the thigh mass was no longer tender to palpation, he started walking, and imaging showed reduction in size and enhancement of the thigh mass (Figs 3B and 3C). In the setting of clinical and radiographic response, erdafitinib treatment was continued with a 50% dose reduction (every other day dosing), given the prior toxicities and surgery was deferred. Treatment was ongoing at the time of this report.

DISCUSSION

In this study, we used the sequencing data from two large pediatric studies to describe the types and frequency of



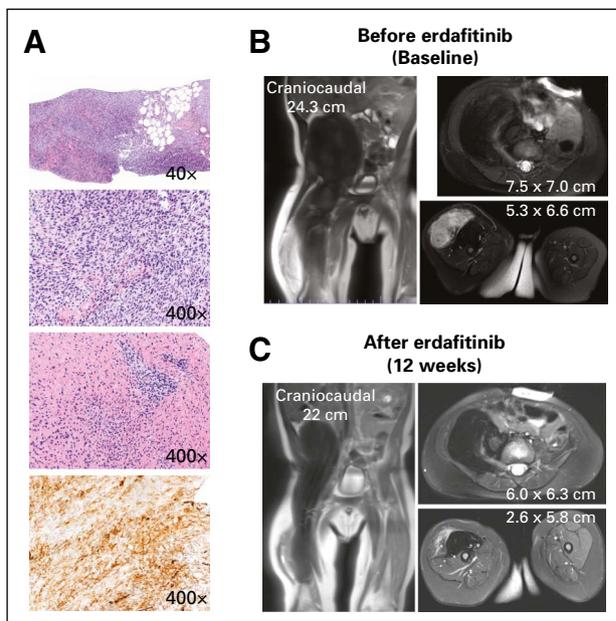


FIG 3. Infant with spindle-cell sarcoma who responded to erdafitinib treatment. (A) Histopathology at diagnosis showing the tumor is mostly hypercellular and infiltrating adipose tissue. Tumor cells are predominantly spindle shaped with foci showing round morphology and occasional intracytoplasmic vacuoles. The pelvic extension of the tumor is relatively less cellular with more collagenized stroma (top three panels; hematoxylin and eosin stain). By immunohistochemistry, tumor cells are diffusely positive for CD34 (bottom panel). MRI (B) at initiation of erdafitinib and (C) after 12 weeks. MRI, magnetic resonance imaging.

actionable *FGFR* alterations identified in pediatric solid tumors. Approximately 3% of pediatric patients across these two cohorts had tumors with an activating *FGFR* alteration and in some cases two alterations, suggesting possible selection for a second alteration for further pathway activation.

We also highlight a proof-of-principle clinical response to an *FGFR* inhibitor in a child with an *FGFR1*-positive soft tissue sarcoma who progressed on lenvatinib. Although two pediatric patients with gliomas have been previously reported in a case series of five patients to show a partial response to the *FGFR* inhibitor, Debio1347, these patients harbored well-characterized alterations including an oncogenic *FGFR1::TACC1* fusion.²⁹ Our study is, to our knowledge, the first to report a pediatric patient with a predicted oncogenic novel *FGFR1* fusion to benefit from targeted therapy. All of these pediatric patients were treated under single patient protocols or with off-label use, highlighting the need for clinical trials investigating *FGFR* inhibitors allowing for a more uniform evaluation of these compounds in pediatric malignancies.

Clinical trial opportunities for pediatric patients with *FGFR*-altered tumors are limited, with only two trials currently enrolling children age < 18 years. Overall, 44% of patients

(18/41) in this study would be potentially eligible for at least one of these two trials, given age and alteration eligibility criteria; however, only 17% of patients (7/41) would have the option of either trial. The 9-month-old patient who responded to off-label erdafitinib did not meet the criteria for any clinical trial despite having an eligible fusion for the Janssen trial. By contrast, the 18-year-old patient with a hotspot *FGFR1* variant would have been eligible for > 20 clinical trials actively enrolling adult patients with solid tumors. If the *FGFR* alterations identified in our cohort had been found in adults, at least 78% (32/41) of the patients would have met the alteration eligibility criteria for an *FGFR* inhibitor clinical trial.

Although three selective pan-*FGFR* inhibitors are FDA-approved, only erdafitinib is in clinical trials enrolling pediatric patients. Newer *FGFR* inhibitors, such as futibatinib, that are able to overcome gatekeeper mutations are now in clinical trials in adults (ClinicalTrials.gov identifier: [NCT02052778](https://clinicaltrials.gov/ct2/show/study/NCT02052778)).³⁰ These *FGFR* inhibitors are important to study in children since the *FGFR4* V550 gatekeeper mutation is frequently identified in pediatric patients with untreated RMS and patients with this mutation are not eligible for the Pediatric MATCH study as they are not expected to respond to erdafitinib. Clinical trials of *FGFR* inhibitors enrolling children are lacking both in number and diversity of *FGFR* inhibitors, highlighting the need to open new *FGFR* inhibitor trials or expand eligibility criteria for ongoing trials to allow enrollment of pediatric patients. The Pediatric Research Equity Act (PREA) was amended in August 2020 to include postmarketing requirements for pediatric studies of molecularly targeted oncology drugs and all New Drug Applications are required to have an Initial Pediatric Study Plan. Infigratinib, an *FGFR* inhibitor approved by the FDA for cholangiocarcinoma, met the postmarketing requirements with a planned pediatric study (ClinicalTrials.gov identifier: [NCT05222165](https://clinicaltrials.gov/ct2/show/study/NCT05222165)). There may be Initial Pediatric Study Plans that we have not reported on as these are not publicly available before FDA drug approval.

This study has several limitations. It is likely that we underestimate the frequency of *FGFR* alterations, especially fusions that can be missed when using a DNA assay. More specifically, the 7% of cases in the cohort (102/1,395) sequenced with OncoPanelv1 were not evaluated for *FGFR2* fusions. In addition, we were stringent in assigning amplification status, which resulted in excluding cases with absolute CN < 7 and those sequenced with OncoPanelv1 and v2 for which absolute CN was not available. Additionally the VUSs, present in 95 patients, were not evaluated with functional studies and some may have been activating. An additional limitation is inclusion of *FGFR* amplification (CN ≥ 7) as an activating alteration as it is difficult to assess the pathogenicity of *FGFR* amplifications. That said, where assessed, *FGFR* expression was higher in *FGFR*-amplified compared with *FGFR*-nonamplified cases. To date, clinical

trial results are unclear regarding whether *FGFR* amplifications are a biomarker for FGFR-TKI response, and whether responses differ between *FGFR* genes and inhibitor used.^{17,31-33} Finally, the infant with a *FGFR1* fusion-positive soft tissue sarcoma who had a response to an FGFR inhibitor had a very short follow up time, so the durability of the response in this patient is yet unknown.

Despite these limitations, to our knowledge, this is the first and largest study of activating *FGFR* alterations in pediatric patients, which identifies an important patient population with overall limited treatment options. We describe the

clinical characteristics of pediatric patients with targetable *FGFR* alterations, including response to an FGFR inhibitor in one patient with a novel fusion. Although *FGFR* alterations are rare, new molecular therapies in development that target FGFR should have early pediatric investigations in accordance with the RACE for Children Act. At a minimum, these trials should include assessment of dosing and liquid formulations. Approaches to address the infrequent occurrence of these alterations in pediatric cancer include international collaboration, prioritization of agents to be studied, and histology agnostic clinical trials.

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PRIOR PRESENTATION

Presented at the AACR Annual Meeting 2022, New Orleans, LA, April 13, 2022.

DATA SHARING STATEMENT

Individual participant data that underlie the results reported in this article, after deidentification, are available in the article and in its online supplementary material.

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