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Review / Derleme

NTRK Somatic Fusions and Tumor Agnostic Treatment in Pediatric Cancers

Çocukluk Çağı Kanserlerinde NTRK Somatik Füzyonları ve Tümör Agnostik Tedavi

Sonay İncesoy Özdemir[1], Ayça Yağmur Şimşek[2], Emel Cabi Ünal[1]

[1]Ankara University, School of Medicine, Department of Pediatrics, Division of Pediatric Oncology, Ankara, Turkey
[2]Ankara University, Faculty of Medicine, Ankara, Turkey

Abstract

Neurotrophic tyrosine receptor kinase (NTRK) gene rearrangements have been recently identified and developed as one of the biomarkers that have been utilized as new targets for cancer therapy. NTRK gene fusions have taken their place in individualized targeted therapy by being used as a predictive (diagnostic) biomarker as well as a treatment target. Selective inhibitors of NTRK fusion proteins have potent efficacy in the treatment of NTRK fusion-positive solid tumors. Detection of these fusions have become important since the finding of new drugs for which U.S. Food and Drug Administration (FDA) granted approval and which are used on the treatment of patients who has NTRK fusions positive cancers. Clinical trials have shown that first generation tyrosine receptor kinase (TRK) inhibitors, larotrectinib (Vitrakvi, Bayer HealthCare Pharmaceutical Inc, New Jersey, U.S.) and entrectinib (Rozlytrek, Genentech Inc, California, U.S.), have potent efficacy in the treatment of cancers harbouring NTRK fusion. In the future, with the increase in the number of comprehensive studies on these drugs further information will become available and beneficial.

Keywords: NTRK fusion, tumor agnostic treatment, precision medicine, larotrectinib, entrectinib.

Öz

Nörotrofik tirozin reseptör kinaz (NTRK) geni yeniden düzenlemeleri yakın zamanda kanser tedavisi için yeni hedefler olarak ortaya konulan biyobelirteçlerden bir tanesi olarak tanımlanmış ve geliştirilmiştir. NTRK gen füzyonları öngörücü (prediktif-tanısal) bir biyobelirteç olarak kullanılmasının yanı sıra tedavi hedefi olarak da kullanılarak bireyselleştirilmiş hedef tedavide yerini almıştır. NTRK füzyon proteinlerinin selektif inhibitörleri, NTRK füzyon pozitif solid tümörlerin tedavisinde güçlü etkinliğe sahiptir (tümör-agnostik tedavi). Tümörlerinde NTRK füzyonları saptanan hastaların tedavisinde etkili olan FDA (Amerika Birleşik Devletleri Gıda ve İlaç Yönetimi) onaylı yeni tedavilerle birlikte, bu füzyonların test edilmesi önemli hale gelmiştir. Yapılan klinik çalışmalar birinci nesil tirozin reseptör kinaz (TRK) inhibitörleri olan larotrectinib ve entrectinibin NTRK füzyonu pozitif kanserlerin tedavisinde yüksek oranda başarılı olduğu görülmüştür. İlerleyen zamanlarda bu ilaçlar üzerine geniş kapsamlı araştırmaların sayısının artması bu ilaçlar hakkında daha fazla bilgiyi mevcut kılacak ve faydalı olacaktır.

Anahtar Kelimeler: NTRK füzyonu, tümör agnostik tedavi, hassas tıp, larotrectinib, entrectinib.

Corresponding *(İletişim)*: Ayça Yağmur Şimşek, Ankara University School of Medicine, Ankara, Turkey
E-mail *(E-posta)*: aycayagmursimsek16@gmail.com
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INTRODUCTION

Precision medicine is often defined as providing the right drug to the right patient at the right time by precisely targeting the molecular pathways that cause disease.[1] In the past few years, since the deepening of our knowledge about cancer biology, signaling pathways and molecules that play a role in the development of many types of cancer have been discovered, important steps have been taken towards individualization of cancer treatment with the determination of the genes responsible for these molecules. The point reached in cancer treatment is to aim to block these oncogenic targets in the cells (tumor-agnostic therapy), regardless of which part of the human body they are located in.[1,2] In contrast of precision medicine tumor-agnostic therapy focuses on targetable genetic differences of a specific cancer type not diffirenceses an individual has which can leed to better treatment such as a person's genetic makeup, or the genetic profile of an individual's tumor. Although these two treatment options overlap when it comes to genetic factors precision medicine targets individual factors but tumor agnastic therapy targets cancer spesific factors. Neurotrophic tyrosine receptor kinase (NTRK) gene rearrangements have been recently identified and developed as one of the biomarkers that have been utilized as new targets for cancer therapy.[3] NTRK gene fusions have taken their place in individualized targeted therapy by being used as a predictive (diagnostic) biomarker as well as a treatment target. Selective inhibitors of NTRK fusion proteins have potent efficacy in the treatment of NTRK fusion-positive solid tumors. Of these agents, larotrectinib (Vitrakvi, Bayer HealthCare Pharmaceutical Inc, New Jersey, U.S.) and entrectinib (Rozlytrek, Genentech Inc, California, U.S.), first generation tyrosine receptor kinase (TRK) inhibitors, have been approved for the treatment of TRK fusion-positive solid tumors, regardless of the tissue from which the cancer originated.[4]

Structure, Function and Oncogenic Potential of NTRK Genes

The NTRK genes consist of three genes, NTRK1, NTRK2, and NTRK3, and are located on chromosomes 1q23, 9q21.33 and 15q25.3, respectively.[5] These genes encode a family of tyrosine kinase receptors that play an active role in neural development. The tropomyosin receptor kinase (TRK) receptor family includes the TRKA, TRKB, and TRKC receptors encoded by the NTRK1, NTRK2, and NTRK3 genes, respectively. All three members of this receptor family consist of an extracellular ligand-binding regoin, a transmembrane regoin, and an intracellular adenosine triphosphate-binding region. These tyrosine receptor kinases are activated when neurotrophin ligands, which are physiologically expressed in human neuronal tissue and play an important role in neuronal development and differentiation, bind to the extracellular region. Neurotrophins are specific to each receptor and activate different intracellular pathways. In particular, nerve growth factor activates TRKA, brain-derived neurotrophic factor and neurotrophin (NTF) 4/5 activates TRKB, and NTF-3 activates TRKC. Receptor homodimerization is triggered by ligand-receptor interaction and when the kinase domain is activated it stimulates the downstream signaling pathway. TRKA and TRKB lead to the activation of MAPK/RAS/ERK, phospholipase C-gamma and phosphatidylinositol 3-kinase (PI3K) pathways. On the other hand, TrkC, which uses NTF-3 as ligand, activates PI3/AKT pathway. These pathways are of vital importance in the development and function of both the central and peripheral nervous systems. NTRK gene fusions are the result of intrachromosomal or interchromosomal rearrangement. The resulting novel fusion oncoprotein is both abnormally expressed and constitutively active, leading to activation of downstream pro-oncogenic pathways.[6,7]

The first evidence of the role of NTRK genes in cancer development dates back 30 years, when NTRK fusions were initially identified in colorectal and thyroid tumors.[8] Since then, NTRK gene abnormalities have been described in several adult and pediatric cancers. Gene fusions are the most well understood form of oncogenic NTRK activation. In fact, single nucleotide changes and gene copy number changes are also sporadically observed, although their clinical significance is less clear. Several fusion partners for NTRK genes have been identified so far. The resulting hybrid genes result from intrachromosomal or interchromosomal rearrangements between the 3' end of the NTRK gene, where the tyrosine kinase domain is located, and the 5' end of the fusion partner, which is a ubiquitously expressed protein that usually contains oligodimerization domains. The result is ligand-independent activation of the tyrosine kinase domain in the aberrantly expressed fusion oncogene.[7-9]

Cancers Harbouring NTRK Fusion

NTRK gene fusions leading to TRKA, TRKB, and TRKC rearrangements have been reported with varying frequencies in multiple solid and hematological malignancies in both adult and pediatric patients, and are detectable in up to 1% of all solid tumors. Tumors can be divided into two main classes: rare cancers with a high frequency of NTRK gene fusion (>80%) and more common cancers with a lower frequency of NTRK gene fusion (5%–25% or <5%). High frequency of NTRK gene fusions have been described in secretory breast and secretory salivary gland carcinomas in adult patients (90-100%) and in infantile fibrosarcomas (91-100%) other mesenchymal tumors (100%) and congenital mesoblastic nephromas (83%) in pediatric patients (**Figure 1**).

NTRK gene fusions are found at a relativly lower frequency in papillary thyroid cancer secondary to radiation in adult patients (14.5%) and in papillary thyroid cancer (26%) and spitzoid tumors (16%) in pediatric/adolescent patients. The reported frequency of NTRK gene fusions in common cancer types; head and neck cancer (0.2%), lung cancer (0.2%-3.3%), colorectal cancer (0.7%-1.5%), melanoma (0.3%) are usually <5%. It occurs at a low incidence in spitzoid melanocytic neoplasms, pediatric midline gliomas (particularly pons

glioma), and KIT/PDGFRA/RAS negative gastrointestinal stromal tumors, and many other solid tumors. A recurrent ETV6-NTRK3 translocation is detected in >75% (up to 90% in some series) cases of infantile fibrosarcoma and congenital mesoblastic nephroma in pediatric patients.[10] Detection of ETV6-NTRK3, initially discovered in infantile fibrosarcoma, has an important role in distinguishing this entity from other pediatric spindle cell tumors. Along with its diagnostic utility, the existence of this translocation has recently led to the successful use of NTRK inhibitors as neoadjuvant and adjuvant for patients with infantile fibrosarcoma. The ETV6-NTRK3 fusion also occurs quite commonly in a subset of radiation-associated and pediatric papillary thyroid carcinomas (PTCs), constituting the most common gene rearrangement after RET-PTC. However, NTRK1 fusions with other fusion partners other than ETV6 have also been described in this tumor group. NTRK1 fusions have been identified as the most common kinase fusions with those involving ROS1 in the entire spectrum of biological spitzoid neoplasms, including benign spitz nevi, atypical spitz tumors, and spitzoid melanomas (**Figure 2**, **Figure 3** and **Figure 4**). The incidence of NTRK1 fusions to be detected with the existance of other kinase fusions (ROS1, ALK1, RET, BRAF) is high.[10]

Methods used to Detect NTRK Fusion Genes

When NTRK gene fusions are considered, the fact that they can be detected at varying rates according to the age group and diagnosis of the patient necessitates the planning of diagnostic algorithms in this direction, considering the principles of sensitized medicine. Various conventional and current technologies are available for testing, including FISH, PCR, DNA and RNA-based next-generation sequencing (NGS). RNA-based next-generation sequencing represents the gold standard for the identification of NTRK fusions, but FISH and DNA-based next-generation sequencing using segmented probes also represent adequate approaches. Immunohistochemistry to detect elevated Trk protein levels may not be a definitive diagnostic methodology on its own, but may be useful as a screening technology for economic feasibility.[11] FISH is the standard method especially for ETV6-NTRK3 fusion and should be applied as a first step in certain diseases. However, it remains a limited method for detecting intrachromosomal fusions such as NTRK1 gene fusions. The NGS-based approach is the ideal method for NTRK fusion detection, especially in patients with advanced disease and small amounts of biomaterial. In this method, the validation and accreditation of the laboratory gains importance.[12]

Tumor Agnostic Treatment

Tumor agnostic therapy is a drug therapy that is used regardless of the tissue from which the tumor originates and the location of the tumor in the body. This therapy requires the presence of a specific molecular alteration that the drug can target. One of these target molecular alterations is TRK receptors seen in cancers harbouring NTRK gene fusions. TRK inhibitors were initially produced as pain relievers.[13]

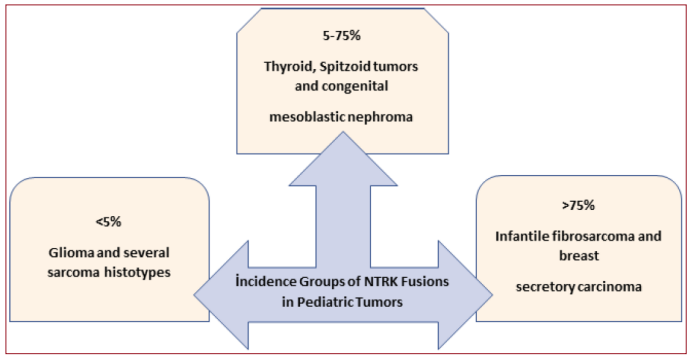

Figure 1. Incidence groups of NTRK fusions in pediatric tumors.

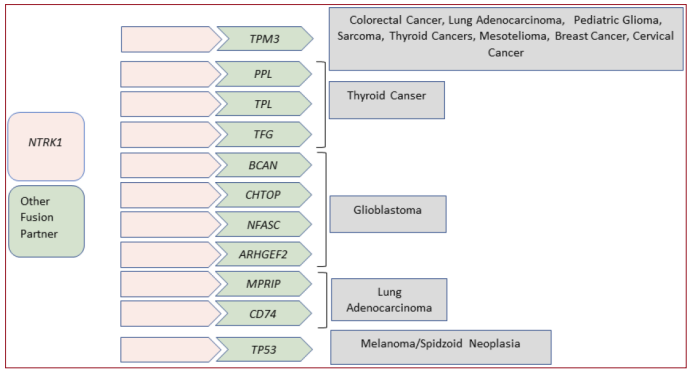

Figure 2. NTRK1 gene fusion derived cancers and the fusion partners

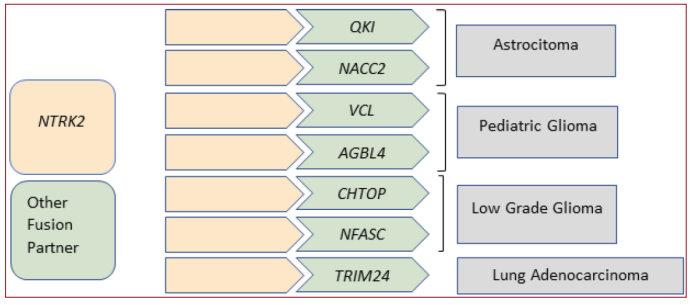

Figure 3. NTRK2 gene fusion derived cancers and the fusion partners

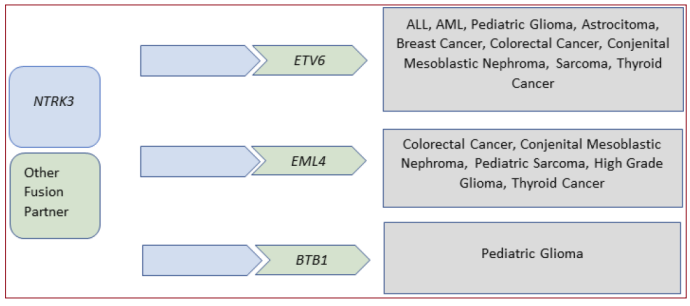

Figure 4. NTRK3 gene fusion derived cancers and the fusion partners

Currently, broad-acting TRK inhibitors and selective TRK inhibitors are important drugs used in the tumor agnostic treatment of cancers hourboring NTRK fusions. First generation TRK inhibitors larotrectinib and entrectinib are the drugs that are used in the treatment of NTRK fusion derived cancers and on which the most comprehensive

studies have been conducted. Entrectinib (Rozlytrek, Genentech Inc, California, U.S.) is a broad-acting inhibitor that effects TRKA/B/C receptors as well as ROS1 and ALK. Larotrectinib (Vitrakvi, Bayer HealthCare Pharmaceutical Inc, New Jersey, U.S.) is a specific inhibitor of TRKA/B/C receptors (**Table 1**).

Table 1. Receptors on which larotrectinib and entrectinib have an inhibitory effect

Effect profile	TRKA	TRKB	TRKC	ALK	ROS1
Larotrectinib	*	*	*		
Entrectinib	*	*	*	*	*

TRKA, tyrosine receptor kinase A receptor; TRKB, tyrosine receptor kinase B receptor; TRKC, tyrosine receptor kinase C receptor; ALK, anaplastic lymphoma kinase; ROS1, ROS protooncogene 1; *, effect is present.

Both drugs inhibit the growth of cell lines and xenografts by downstream inhibition of the MAPK, PI3K–AKT, PKC and STAT3 pathways.[4,13]

Larotrectinib

Larotrectinib is a highly-selective, pan-Trk inhibitor. It inhibits the adenosine triphosphate binding site of TrkA, TrkB, and TrkC, with half maximal inhibitory concentration (IC50) values in the low nanomolar range (5–11 nM).[13,14] The first clinical trial on larotrectinib was a dose finding-study conducted in 2014. In this study, patients were not required to have an NTRK fusion positive cancer. The results of the study were published in 2015 and described a patient with a nearly complete response to treatment. Data from the study was the first data on the preclinical and clinical features of larotrectinib. Phase trials began to be designed specifically on NTRK gene fusion positive patients after the results of the dose-finding study are announced.[15]

Phase I trial (NCT02122913) which includes 75 adult patients, Phase I/II trial which includes 174 pediatric patients (NCT02637687, SCOUT), and Phase II basket trial which includes 200 pediatric/adult patients (NCT02576431, NAVIGATE) were conducted in order to evaluate larotrectinib.[14,15] 55 patients from previous three phase trials aged between 4 months and 76 years, with 17 different cancer diagnoses has been analyzed regardless of tumor type, patient age, and NTRK fusion character. The overall response rate to treatment was 80% (95% CI, 67 to 90), and the median response time was 1.8 months.[14] Another pooled analysis of 175 patients with NTRK fusion driven cancers from the previous three phase trials has shown time to response for larotrectinib ranged from 0.9 to 6.6 months, with a median time to response of 1.8 months; 12-month and 24-month durations of response were 81 % and 66 %, respectively with an objective response rate of 78%, independent of tumor histology, age, and/or NTRK gene fusion status.[14,16]

Larotrectinib has been shown to cross blood/brain barrier and is effective in central nervous system tumors with a disease control rate at ≥24 weeks of 63%. Larotrectinib was approved by the FDA on 26 November 2018 for use in adults and children in NTRK fusion-positive solid tumors.[17] Larotrectinib is available in oral liquid (20 mg/mL) and capsule (25 and 100 mg) formulations. Recommended dosage is two 100 mg doses a day for adults and two doses of 100 mg/m^2 a day for children (with a maximum dose of 100 mg).[14]

During the studies, tumor size reduction was achieved to allow limb sparing surgery in 2 children with locally advanced fibrosarcoma. In the follow-ups after operations with negative surgical margins, larotrectinib treatment was stoped and no progression was observed.[18] Global, prospective, multi-cohort, non-interventional phase IV study (NCT04142437, ON-TRK) which ment to be completed in March 31 2030 is currently recruiting patients in order to collect real-world efficacy and safety data for larotrectinib.[14,19]

Entrectinib

Entrectinib is a TRK inhibitor that has been proven to be effective in cancers caused by mutations in NTRK1/2/3, ALK and ROS1 genes.[13,20,21] Inhibition of TRK, ROS1 and ALK leads to inhibition of downstream signalling pathways, including phospholipase C gamma, mitogen-activated protein kinase and phosphoinositide 3 kinase/protein kinase B, which in turn leads to inhibition of cell proliferation and induction of tumour cell apoptosis. Entrectinib has been proven to cross blood/brain barrier and is affective in central nervous system tumors.[22]

Four phase trials were conducted to evaluate the clinical features of entrectinib, adult phase I trial (ALKA-372-001), adult phase I trial (STARTRK-1), phase II basket trial (STARTRK-2) and pediatric phase I/IIb trial (STARTRK-NG). Studies have shown that the objective response rate of entrectinib is 58% (43 to 71), the median response time is 10.4 months, progression-free survival is 11.2 months, and overall survival is 20.9 months.[13] On August 15, 2019, entrectinib received FDA approval for use in adults and children older than 12 years in the treatment of NTRK fusion-positive solid tumors.[23] Recommended dosage is 600 mg a day for adults, and 300 mg/m2 for children aged 12 years or older, until disease progression or unacceptable toxicity.[22] During the studies, significant tumor and metastasis regression was observed after 1 month of treatment in a 20-month-old child with infantile fibrosarcoma and central nervous system metastases.[21,24]

A case report published on the Infant with germline ALKAL2 variant and refractory metastatic neuroblastoma with chromosomal 2p gain and anaplastic lymphoma kinase and tropomyosin receptor kinase activation showed that partial response was obtained and persistent metastases were still existed, although two different treatment regimens were tried in a scale of time. Because the patient was too young for the ongoing entrectinib RXDX-101-03 trial (inclusion age 2-22 years, NCT02650401), compassionate use was granted

by the study sponsor, Ignyta Inc. Treatment with entrectinib started at an oral dose of 200 mg/day (393 mg/m2) once daily, increasing to 300 mg (475 mg/m2) and 400 mg (540 mg/m2) once daily after 10 and 29 months, respectively. After two months of entrectinib treatment, significant regression of metastases and improvement in general condition were observed. In the ongoing follow-ups, it was observed that the metastases regressed at a level that could not be detected by MRI. The child, who has reached the age of 4, is still on entrectinib and celecoxib treatment, and his general condition has been reported to be good.[25]

Safety and Adverse Effect Profile

Studies regardless of molecular structure and cancer type have mostly been conducted on first generation TRK inhibitors (larotrectinib and entrectinib) and have shown that these two agents have favorable toxic profiles. The treatment-emergent adverse effects are believed to be the result of the inhibition of normal TRK receptors, which are not a product of a mutant gene, that has serius affects on embryonic central nervous system development and neural activity. These side effects have been mostly (>90%) reported in grade 1 and grade 2 severity, and the relatively common ones are dizziness (for larotrectinib: 16-25% for entrectinib: 16-25%), paresthesia (for larotrectinib: ~19% for entrectinib: unclear), weight gain (for larotrectinib: 15% for entrectinib: ~19%) and changes in consciousness (Common Terminology Criteria For Adverse Effects). It has been reported that weight gain is more common in the pediatric age group (for larotrectinib: 18% for entrectinib: 28%).[13] Dose reductions due to larotrectinib treatment-related adverse events were reported in 11% of NTRK gene fusion-positive patients and discontinuations in 2%. No treatment-related deaths were reported.[14,16] Unacceptable toxicity is a treatment terminating factor for entrectinib.[22]

TRK Inhibitor Resistance

Two pathways of resistance have been observed in patients receiving TRK inhibitor therapy. These pathways can be classified as on-target resistance and off-target resistance. Resistance has been observed in the use of both larotrectinib and entrectinib.

On-target resistance relies on genomic changes that cause the release of mediators that bind to TRK receptors. Mutation in the kinase regions results in the formation of amino acids consisting of three regions: the solvent front, the gatekeeper residue or the xDFG motif. These amino acids act by preventing drugs from binding to TRK receptors.

Off-target resistance, which is another resistance pathway, acts by creating alternative TRK receptors and downstream signaling pathway mediators via MET amplification, BRAFV600E mutation, KRAS mutation or IGF1R activation as seen in ALK and ROS1 fusions (On and off target resistance mechanisms are shown in **Figure 5**).[13]

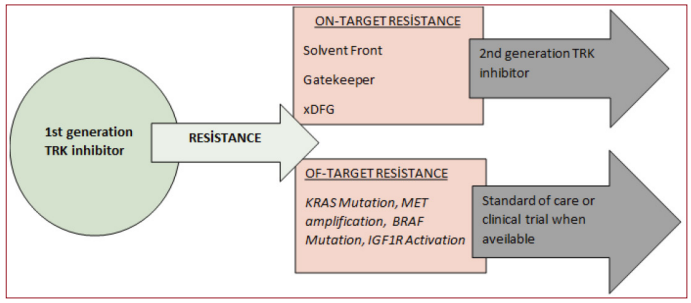

Figure 5. On and off target resistance mechanisms

CONCLUSIONS

TRKA/B/C receptors expressed by NTRK1/2/3 genes are significant to development of the central nervous system and neural activity via downstream signaling pathways mediated by neurofins. Various fusions occurring in the NTRK1/2/3 gene regions cause the formation of uncontrolled TRK receptors. Mutagenic TRK receptors are involved in the pathogenesis of many different types of solid tumors. TRK inhibitor therapy targets TRK receptors and has been used in adult and pediatric solid tumors harbouring NTRK fusion in recent years. TRK inhibitor therapy has shown successful results. In phase studies, results were obtained in terms of treatment response, tolerability and toxicity, and FDA approvals were granted.

It is shown in the previous stadies that in existance of TRK, ALK and ROS1 expression tumor agnostic therapy is favorible. Tumor agnostic treatment has it's adventages in terms of overall respond rate and toxic profile in certain cancer types. Although phase studies on the effects of tumor agnostic treatment in pediatric age groups have favorable results, the remaining limited number of clinical studies are case based studies on small patient groups. In the future, further extensive clinical studies with higher number of participants and comprehensive data on the use of TRK inhibitor therapy in pediatric age groups are neccessary.

ETHICAL DECLARATIONS

Referee Evaluation Process: Externally peer-reviewed.
Conflict of Interest Statement: The authors have no conflicts of interest to declare.
Financial Disclosure: The authors declared that this study has received no financial support.
Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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