Title

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Journal

The American Journal of Managed Care, 28(2 Suppl)

ISSN

1088-0224

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Publication Date

2022

DOI

10.37765/ajmc.2022.88834

Peer reviewed

Published in final edited form as:

Am J Manag Care. 2022 January ; 28(2 Suppl): S15–S25. doi:10.37765/ajmc.2022.88834.

Diagnosis and Management of TRK Fusion Cancer

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Abstract

The tropomyosin receptor kinase (TRK) family of proteins is encoded by neurotrophic tyrosine receptor kinase (*NTRK*) genes and has a role in the development and normal functioning of the nervous system. *NTRK* gene fusions have been identified as oncogenic drivers in a wide range of tumors in both adult and pediatric patients. There has recently been a paradigm shift in cancer treatment toward biomarker-based targeted therapies, as an increasing number of actionable targets are being identified across different tumors and/or tumor histologies. These targeted agents offer greater comparative effectiveness and safety vs historical nontargeted standard therapies. The development of drugs that specifically target oncogenic drivers of cancer has led to the emergence of screening technologies to identify the patients most likely to benefit from targeted therapy. This review describes the role of *NTRK* gene fusions in cancer and outlines the epidemiology of *NTRK* gene fusions, the therapeutic benefits of targeting TRK fusions with small molecule inhibitors, and recommendations for *NTRK* gene fusion testing in adult and pediatric patients with cancer, in order to guide treatment decisions.

Overview of *NTRK* Gene Fusions

The neurotrophic tyrosine receptor kinase (*NTRK*) genes *NTRK1*, *NTRK2*, and *NTRK3* encode the tropomyosin receptor kinase (TRK) family of proteins: TRKA, TRKB, and TRKC, respectively.[1] Neurotrophins were initially identified as survival factors for sensory and sympathetic neurons, but they are now understood to play many roles in the development and functioning of the nervous system.[1–3] TRK receptors are predominantly expressed in neuronal tissue, and their activation has a significant impact on a variety of neuronal events, such as cell differentiation and survival, proliferation, and synaptic

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Authorship information: Analysis and interpretation of data (SK, AI, MSB, JJC, SDS, UL, NF); drafting of the manuscript (SK, AI, MSB, JJC, SDS, UL, NF); critical revision of the manuscript for important intellectual content (SK, AI, MSB, JJC, SDS, UL, NF).

formation.[1,3] The precise regulation of TRK receptors and their activation is therefore critically important for normal cell functioning.

NTRK gene fusion events that occur between *NTRK1*, *NTRK2*, or *NTRK3* and various unrelated gene partners have been identified in cancer. These typically arise from fusion of the 3' region of an *NTRK* gene (containing a functional kinase domain) and the 5' region of an unrelated gene, either by intra- or inter chromosomal rearrangement. The resulting chimeric oncogenic gene fusion encodes a protein containing the N-terminus of the fusion partner joined to the C-terminus of the TRK protein, including the catalytic tyrosine kinase domain. This results in a protein that retains kinase activity, is ligand independent, and is constitutively activated to drive cell and tumor development.[1,4] One of the most common and best characterized *NTRK* gene fusions is *ETV6-NTRK3* (Figure 1),[5] which is found in the majority of salivary gland secretory carcinomas, secretory breast cancers, and infantile fibrosarcomas.[5–8] However, an array of different *NTRK* gene fusion partners have been detected, with novel fusion partners being regularly discovered. One study found 88 unique fusion partner pairs among 889 patients with TRK fusion cancer.[9]

Technologies for the Detection of *NTRK* Fusions

The development of drugs that specifically target oncogenic drivers of cancer has led to the emergence of screening technologies to identify the patients most likely to benefit from targeted treatment.

Approaches that may be used to detect *NTRK* gene fusions in clinical tissue samples, either indirectly or directly, include immunohistochemistry (IHC), fluorescence in situ hybridization (FISH), reverse transcriptase polymerase chain reaction (RT-PCR), and next-generation sequencing (NGS) of DNA and/or RNA (Table 1).[5] IHC may be used to detect TRK overexpression as a surrogate for the presence of an *NTRK* gene fusion, and it is a useful screening tool in clinical settings with limited access to NGS platforms.[5] IHC has proved to be a time- and tissue-efficient technique for routine screening[10] and is attractive due to the low cost and universal availability compared with other technologies; however, some studies have reported challenges in the interpretation of IHC data.[11] In particular, the specificity of IHC in central nervous system tumors can be limited due to high background TRK expression in neural tissues.[12] As such, internal controls (eg, endothelial cells) and confirmatory testing using a molecular method are often recommended.[5] FISH and RT-PCR, often used for testing tumor types with a high prevalence of *NTRK* gene fusions, are quick and cost-efficient but are able to detect only known, specific fusions.[5,11] For FISH, a separate break-apart probe is required for each of the 3 *NTRK* genes, and the 5' gene fusion cannot be identified using this method; furthermore, FISH does not confirm whether the fusion gene is transcribed.[11] RT-PCR can be an alternative or complementary approach to FISH, detecting *NTRK* gene fusions using primers in the coding sequence of the 5' fusion partner and the *NTRK* kinase domain. However, the large number of potential 5' fusion partners may make a comprehensive multiplex RT-PCR assay challenging.[11,13] Although DNA-based NGS allows for many genomic events to be interrogated, a disadvantage is that when gene translocations are detected, it is difficult to determine if these result in functionally expressed fusions. DNA-based NGS is also less accurate in detecting gene

fusions that involve large intronic regions.[11] RNA-based NGS is the preferred approach due to the diverse array of reported gene fusion partners in cancer. In addition to having the ability to detect multiple genomic alterations in a single assay, RNA-based NGS is a precise, specific, and highly sensitive testing modality.[11,13] However, it can be limited by RNA quality. Moreover, NGS generally is not always accessible in a clinical setting and may require relatively long turnaround times.

Based on current technology, an optimal approach to use at initial diagnosis may be tissue DNA-based NGS, complemented with RNA-based NGS. For tumors such as salivary gland secretory carcinomas and infantile fibrosarcomas that have a high prevalence of *NTRK* gene fusions, more specific and limited techniques that have already been described may also be appropriate.

Epidemiology of *NTRK* Gene Fusions

NTRK gene fusions are oncogenic drivers of various adult and pediatric cancers.[1,3,6,14,15] Incidence and prevalence data for *NTRK* gene fusions have only recently become available due to the increased availability of NGS and molecular testing techniques.[1] Overall, solid tumors with *NTRK* gene fusions are rare. In 2018, the overall global incidence was estimated to be 0.52 per 100,000 persons, and the overall 5-year prevalence was estimated to be 1.52 per 100,000 persons, based on a systematic review and meta-analysis.[16] *NTRK* gene fusions are found at very low frequencies in more prevalent tumor types, such as lung (0.2%; 95% CI, 0.1%-0.3%) and colorectal cancer (CRC) (0.3%; 95% CI, 0.2%-0.4%). However, they are common in several rare tumors, including infantile fibrosarcoma (90.6%; 95% CI, 67.4%-100%), secretory breast carcinoma (92.9%; 95% CI, 72.6%-100%), salivary gland secretory carcinoma (79.7%; 95% CI, 62.8%-96.5%), and congenital mesoblastic nephroma (21.5%; 95% CI, 13.1%-32.2%) (Table 2).[16] *NTRK* gene fusion events appear to arise more commonly in the *NTRK1* and *NTRK3* genes, with the exception of primary brain tumors, in which fusions occur more commonly with *NTRK2*.[1,17] *NTRK* gene fusions are also reported to occur more frequently in pediatric tumors than in adult tumors.[18]

Real-world Evidence on TRK Fusion Cancer

Despite significant progress in treating TRK fusion cancer, there were, until recently, limited data on the demographics, genomic characteristics, and natural history of TRK fusion cancer compared with cancers not harboring *NTRK* gene fusions. This has partly been due to the rarity of TRK fusion cancer and the technical limitations and variation over time of detection methods.[19,20] A number of real-world studies have been conducted to investigate the co-occurrence of other biomarkers and the overall prognosis of patients with TRK fusion cancer.

Co-occurrence of *NTRK* Gene Fusions and Other Actionable Biomarkers

Voyager-1 was a retrospective matched cohort study; it included information on patients with solid tumors gathered from a database of deidentified electronic health records from more than 280 cancer clinics, across approximately 800 US sites. Data included clinical and demographic characteristics, treatment patterns and outcomes, and genomic data such as

somatic mutations, copy number alterations, genomic rearrangements, and microsatellite instability (MSI) status.[20] Voyager-2 linked genomic data from the United Kingdom's 100,000 Genomes Project with clinical data from UK cancer databases.[21] Results of the 2 studies indicated that co-occurrence of oncogenic alterations in *ALK*, *BRAF*, *ERBB2*, *EGFR*, *ROS1*, and *KRAS* was uncommon in patients with *NTRK* gene fusions, supporting the hypothesis that *NTRK* gene fusions are the primary oncogenic drivers in tumors that harbor them, thus highlighting the importance of identifying patients with TRK fusion cancer. Furthermore, results of another study using a large real-world database of comprehensive genomic profiling data have demonstrated a lack of correlation between the presence of *NTRK* gene fusions and other clinically actionable biomarkers, including no co-occurrence with known oncogenic drivers in breast cancer and CRC.[9] Given the low likelihood of other co-occurring oncogenic alterations in patients with *NTRK* gene fusions, treatment with a therapy that targets TRK is likely to provide the greatest benefit while avoiding off-target adverse events (AEs). These real-world database studies also showed that both high tumor mutational burden (TMB) and high MSI were more frequent in patients with CRC harboring *NTRK* gene fusions than in those who did not. Patients with CRC who test positive for high TMB and/or high MSI could therefore be considered an enriched population for *NTRK* gene fusions. These data align with previous reports that *NTRK* gene fusions occur more frequently in MSI-high CRC than in microsatellite stable CRC.[22] Rosen et al also reported that *NTRK* gene fusions appear to be more common in tumors lacking canonical drivers, which, they concluded, may partially explain the tumor-agnostic efficacy of TRK inhibitors.[19]

Natural History of TRK Fusion Cancer

Several retrospective studies, including Voyager-1 and Voyager-2, have evaluated the prognostic impact of *NTRK* gene fusions. The results from these studies suggest that the prognosis of patients with and without *NTRK* gene fusions is similar, with some studies showing a trend (albeit not statistically significant) toward worse prognosis in patients with TRK fusion cancer.[20,21,23–25] Therefore, the outcomes observed in patients with TRK fusion cancer receiving larotrectinib or entrectinib in clinical trials (discussed later) can be considered a direct result of TRK inhibition and not due to the patients' inherent prognosis.

Treatment Options for TRK Fusion Cancer

Cancer treatment has historically been based on tumor histology and the tissue of origin.[26] However, the introduction of precision oncology therapies has led to a paradigm shift, with drug development programs migrating away from histology-specific patient selection to biomarker-driven, tumor-agnostic enrichment, with a number of targeted therapies receiving tumor-agnostic regulatory approvals (eg, pembrolizumab in tumors of any type with high MSI).[26,27] Larotrectinib and entrectinib are first-generation TRK inhibitors, approved for the treatment of TRK fusion cancer regardless of tumor type (Table 3).[28,29] Several next-generation TRK inhibitors are already in clinical development.

Overview of Larotrectinib

Larotrectinib is approved in more than 40 countries, including the United States, for adult and pediatric patients of all ages with TRK fusion cancer; it is available in both capsule and liquid formulations.[3,28,30–32] It is a highly selective and potent inhibitor of TRKA (IC_{50} 6.5 nM), TRKB (IC_{50} 8.1 nM), and TRKC (IC_{50} 10.6 nM), with high binding affinity to all 3 receptors (more than 100-fold higher selectivity against a panel of other kinases).[33] It also inhibits the growth of cells and xenografts harboring *NTRK* gene fusions.[26]

The larotrectinib clinical development program is unique, as it encompassed patients across the age spectrum, including children aged as young as 1 month, and with a wide range of tumor types. The efficacy and safety of larotrectinib was evaluated in 3 phase 1/2 clinical studies in adults and children with TRK fusion cancer, who received doses of 100 mg (adults) or 100 mg/m^2 (children) twice daily; these were an adult phase 1 study (NCT02122913) and the SCOUT (NCT02637687) and NAVIGATE (NCT02576431) trials.[30,34] The objective response rate (ORR) from a pooled analysis of these 3 studies (N = 55) was 75% (95% CI, 61%-85%) per independent review and 80% (95% CI, 67%-90%) per investigator assessment, with responses seen regardless of age, tumor type, specific *NTRK* gene, or fusion partner. At 1 year, 71% of the responses were ongoing and 55% of patients were progression free. The majority of AEs were grade 1/2, and there were no treatment discontinuations due to AEs.[30] In an expanded data set of 218 patients with TRK fusion cancer, the investigator-assessed ORR was 75% (95% CI, 68%-81%)(Table 3),[28,29] and median duration of response (DOR) was 49.3 months (95% CI, 27.3 to not estimable [NE]).[35] Median progression-free survival (PFS) was 35.4 months (95% CI, 23.4–55.7), and median overall survival (OS) was not reached.[35] Responses were seen with larotrectinib across the spectrum of tumor types included in the study (Figure 2A).[35] The clinical benefits of larotrectinib are illustrated in Figure 3[36] and Figure 4. Treatment-related AEs (TRAEs) observed in larotrectinib clinical trials were predominantly of grade 1/2; grade 3/4 TRAEs were reported in 18% of patients, the most common of which were decreased neutrophil count (7%), increased alanine aminotransferase (3%), and increased aspartate aminotransferase (2%).

Patients across the age spectrum—from infants to the elderly—who received larotrectinib experienced rapid, sustained, and clinically meaningful improvements in quality of life (QOL); these improvements began within 2 months in more than two-thirds of patients.[36,37] QOL scores for most patients were either maintained within or moved into the normal healthy range during larotrectinib treatment.[36] Among patients with TRK fusion cancer who had QOL below normal at baseline and were treated with larotrectinib, 91% of adults and 67% of children 2 years or older moved into the normal/above-normal QOL range following treatment.[37] Sustained QOL improvements occurred within 2 months in 69% of adults and 75% of children 2 years or older and were maintained for a median duration of 12.0 months (range, 1.7–20.3) and NE (range, 1.1–23.0), respectively. With improving survival rates and increasing long-term treatment, patient-reported QOL is a particularly relevant goal to strive for, allowing patients to live both longer and better.

Overview of Entrectinib

Entrectinib, a multikinase inhibitor that targets TRK, ALK, ROS1, and JAK, is approved in the United States and the European Union for adult and pediatric patients 12 years or older with locally advanced or metastatic TRK fusion cancer; it is available in a capsule formulation.[29,38,39]

In vitro, entrectinib inhibits TRKA (IC_{50} 2 nM), TRKB (IC_{50} 0.57 nM), and TRKC (IC_{50} 1.1 nM). It induces potent antiproliferative and apoptotic effects, as well as cell cycle arrest, in various tumor cell lines driven by *NTRK* gene fusion. We see inactivation of downstream AKT and ERK, in addition to antitumor activity and tumor regression, in mouse tumor models harboring *NTRK* fusions.[40]

The efficacy and safety of a once-daily 600-mg dose of entrectinib was evaluated in 4 phase 1/2 clinical trials that included patients with metastatic or locally advanced TRK fusion cancer: ALKA-372–001 (EudraCT 2012–000148–88), STARTRK-1 (NCT02097810), STARTRK-2 (NCT02568267), and STARTRK-NG (NCT02650401). In an initial data set of 54 patients, 31 (57%; 95% CI, 43.2%-70.8%) had an objective response (Table 3[28]).[29,41] Median DOR was 10 months (95% CI, 7.1-NE), median PFS was 11 months (95% CI, 8.0–14.9), and median OS was 21 months (95% CI, 14.9-NE). The most common grade 3/4 TRAEs were increased weight (10%) and anemia (12%), and the most common serious TRAEs were nervous system disorders (4%). Treatment discontinuation due to TRAEs occurred in 4% of patients.[41] In an expanded data set of 121 patients, ORR was 61%, median DOR was 20.0 months, median PFS was 13.8 months, and median OS was 33.8 months.[42]

In terms of patient-reported QOL, global health status remained stable in patients with TRK fusion cancer who were treated with entrectinib during the phase 2 basket trial STARTRK-2.[43] Trends toward clinical improvement were seen for role and physical functioning during treatment, and treatment- and tumor-related symptoms (eg, nausea and fatigue) remained generally stable or trended toward clinically meaningful improvement.

Next-Generation TRK Inhibitors

Acquired resistance to first-generation TRK inhibitors can arise from secondary mutations within the *NTRK* gene kinase domain (on-target resistance), including solvent-front substitutions and gatekeeper mutations, or activation of bypass signaling mechanisms (off-target resistance). Next-generation agents are being developed to address on-target resistance that is mediated by such emergent kinase domain mutations, while maintaining potency against wild-type TRK fusion proteins. The most advanced agents, selitrectinib and repotrectinib, are in phase 1/2 development, and preliminary data suggest encouraging clinical activity. Among patients who had progressed or were intolerant to at least 1 prior TRK inhibitor, selitrectinib treatment resulted in a 34% ORR.[44] The ORR was greater (45%) among patients with confirmed TRK kinase domain mutations. Although some data show that repotrectinib, a ROS1/TRK/ALK tyrosine kinase inhibitor, can overcome acquired resistance to prior TRK inhibition, evidence remains limited so far, generally relating only to single patients.[45–47] Several other next-generation TRK inhibitors are under

early investigation in patients with *NTRK* gene fusions; these include multikinase inhibitors (cabozantinib, merestinib, and sitravatinib) and the ROS1/TRK tyrosine kinase inhibitor taletrectinib (DS-6051b).[48,49]

Clinical Practice Recommendations for TRK Fusion Cancer

Integration of *NTRK* gene fusion testing into routine clinical practice and selection of the optimal testing modality is challenging. Several guidelines have been published that make recommendations on both the diagnosis and treatment of TRK fusion cancer.

Diagnosis

The European Society for Medical Oncology (ESMO) states that the development of optimal approaches to detect human cancers that harbor activating *NTRK1/2/3* fusions is crucial to the administration of TRK inhibitors. In tumors in which *NTRK* gene fusions are highly recurrent, FISH, RT-PCR, or RNA-based NGS is recommended, whereas RNA-based NGS or IHC screening followed by sequencing is considered appropriate for testing an unselected population where fusions are uncommon.[50] ESMO guidelines also advise that the choice of assay and final diagnosis should consider the resources and clinical context.[50]

Penault-Llorca et al proposed a screening algorithm for identifying patients with TRK fusion cancer in clinical practice, in order to guide treatment decisions.[5] The algorithm categorizes tumors based on the incidence of *NTRK* gene fusions, and it incorporates the strengths and availability of each testing modality (Figure 5).[5] In tumors with a high frequency of *NTRK* gene fusions, FISH or pan-TRK IHC (if FISH is unavailable) is recommended, with confirmation by targeted NGS in patients with positive IHC.[5] The pattern of TRK staining by IHC can inform the selection of confirmatory test, as tumors harboring *NTRK1* rearrangements typically show strong, diffuse cytoplasmic staining.[5] In contrast, tumors harboring *NTRK3* rearrangements may have focal nuclear staining but weaker expression.[5] Negative results from FISH or IHC should also be confirmed by NGS. In solid tumors that often harbor various gene fusions, but with a low frequency of *NTRK* gene fusions (5%-25%), an NGS panel that includes *NTRK* fusions is recommended. Lastly, for tumors with a very low frequency of *NTRK* gene fusions (< 5%) but in which molecular screening is common, inclusion of *NTRK* genes in routine NGS analysis is recommended. If NGS is not available or is not routinely utilized, pan-TRK IHC should be used for screening, followed by NGS confirmation of positive results, with RNA-based NGS being the preferred modality. Pan-TRK IHC alone is not sufficient to identify TRK fusion cancer; this is because IHC detects both wild-type and fusion TRK proteins, is associated with false-positive results, and will also detect TRK overexpression resulting from other *NTRK* gene alterations, such as amplification, which may not be primary oncogenic drivers.

Treatment

Larotrectinib and entrectinib are increasingly being integrated into national and international clinical practice guidelines. Clinical practice guidelines from the American Society of Clinical Oncology and ESMO recommend both agents for the treatment of progressive

metastatic solid tumors with *NTRK* fusions, including non–small cell lung cancer, breast cancer, soft tissue sarcoma, salivary gland cancer, and thyroid cancer.[51–56]

Summary

There has recently been important progress in the treatment of cancer based on tumor genomics rather than the tissue of origin. In the case of TRK fusion cancer, the inhibition of the TRK signaling pathway has been found to be an effective approach for cancer treatment in adult and pediatric patients. Although *NTRK* gene fusions are generally rare, they can be found in very prevalent tumors. As such, identifying patients with TRK fusion cancer allows them to potentially benefit from TRK inhibitors, which are highly effective and well tolerated. The therapeutic benefit to these patients outweighs the difficulties of identifying *NTRK* gene fusions. As such, *NTRK* gene fusion testing should be considered in patients with advanced solid tumors, regardless of tumor histology. A number of cancer clinical guidelines include recommendations for *NTRK* gene fusion testing, and testing algorithms have been developed for identifying patients with TRK fusion cancer in clinical practice. The long-term effects of TRK inhibition in pediatric and adolescent patients are currently unknown, but they warrant attention due to the role of TRK signaling in the development and functioning of the nervous system. Resistance to first-generation inhibitor treatment can also arise; therefore, the development of next-generation TRK inhibitors is under way.[26] ■

Acknowledgments

Medical writing support was provided by Michael Sheldon, PhD, and editorial support was provided by George Chappell, MSc, both of Scion (London, UK), supported by Bayer according to Good Publication Practice guidelines. Bayer was involved in fact-checking information provided in the manuscript. However, ultimate responsibility for opinions, conclusions, and data interpretation lies with the authors.

Funding source:

This article was published as part of a supplement that was financially supported by Bayer HealthCare Pharmaceuticals, Inc. Noah Federman's research is supported by NIH National Center for Advancing Translational Science (NCATS) UCLA Clinical & Translational Science Institute (CTSI) Grant Number UL1TR001881.

Author disclosures:

Dr Brose, Dr Carlson, Dr Federman, Dr Kummar, Dr Lassen, and Dr Sullivan have been part of consultancies or paid advisory boards with Bayer. Dr Brose and Dr Federman have been part of consultancies or paid advisory boards with Loxo Oncology. Dr Brose has also been part of consultancies or paid advisory boards with Genentech, AstraZeneca, and Eli Lilly and Company. Dr Brose has received honoraria from Clinical Care Options, Medscape, OncLive®, and PeerView. Dr Brose has also disclosed that research support to the University of Pennsylvania School of Pharmacy has been provided by Bayer, Loxo Oncology, Genentech, Eisai, Blueprint Medicines, Eli Lilly and Company, and Novartis. Dr Carlson has received honoraria from Adaptive Biotechnologies. Dr Federman has received lecture fees for speaking at the invitation of Bayer and received patent royalties from NanoValent Pharmaceuticals, Inc. Dr Federman has also disclosed that he holds stock in the for-profit health care companies Genmab, Reata Pharmaceuticals, and bluebird bio, Inc. Dr Italiano and Dr Lassen have both received grants from Roche. Dr Italiano has also received grants from AstraZeneca, Bayer, Merck, Merck Sharp & Dohme, and PharmaMar. Dr Italiano has disclosed that he has received honoraria from Bayer, Daiichi Sankyo, Epizyme, Ipsen, Roche, and SpringWorks Therapeutics. Dr Kummar has been part of consultancies or paid advisory boards with Boehringer Ingelheim, SpringWorks Therapeutics, Gilead, EcoR1 Capital, Seagen, Mundipharma, Mirati Therapeutics, Genome & Company, and Harbour Biomed. Dr Kummar has also disclosed that she is the cofounder and is an equity holder for PathomIQ. Dr Kummar has also disclosed that she is the editor-in-chief of *Current Problems in Cancer* (Elsevier) and that her spouse is a scientific adviser for Cadila Pharmaceuticals Ltd and is the founder of Arxeon Inc. Dr Lassen has also reported that he has been part of consultancies or paid advisory boards with Pfizer and Novartis. Dr Lassen has also received grants from Bristol Myers Squibb, GlaxoSmithKline, and Pfizer.

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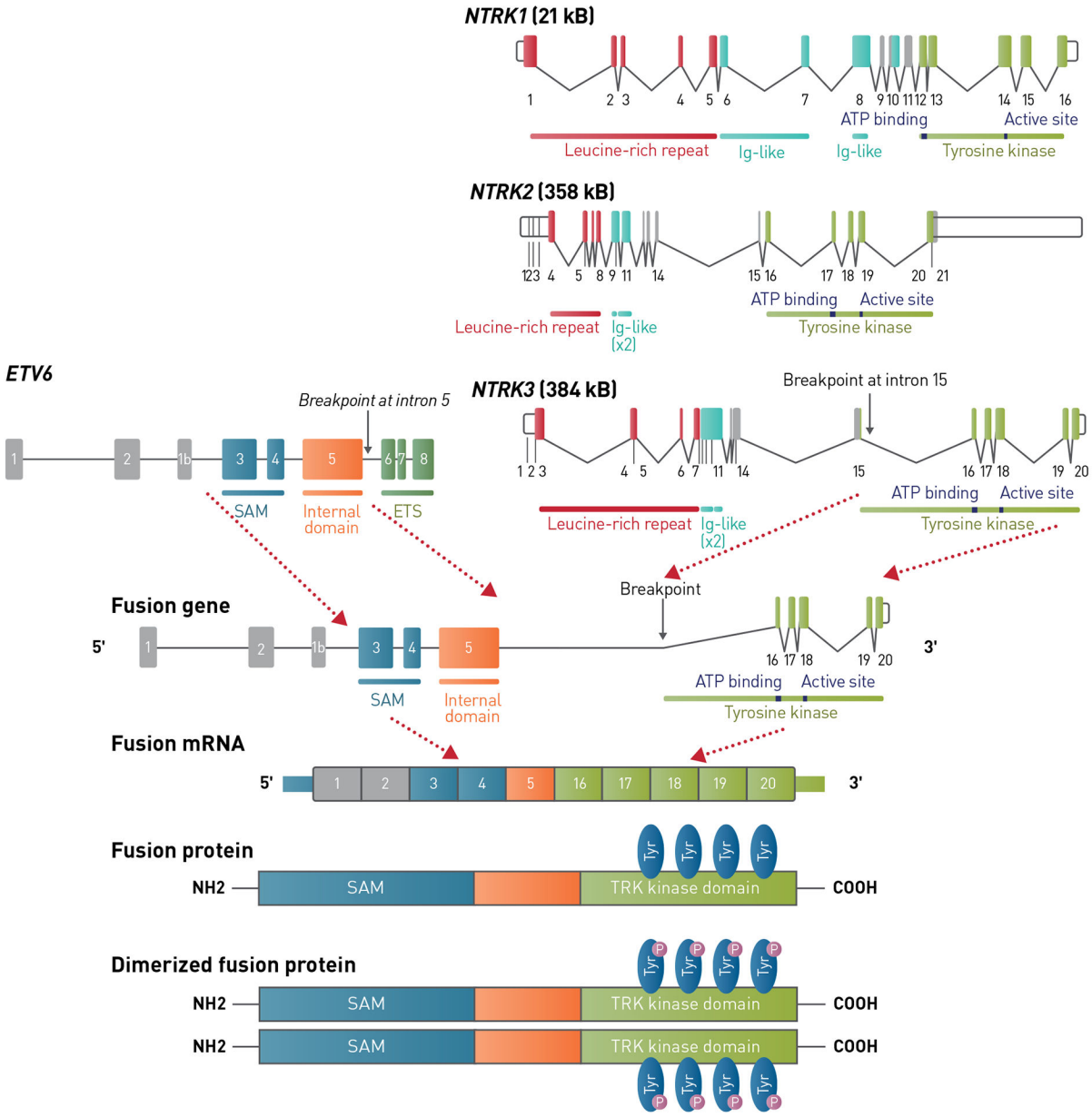

FIGURE 1.

ETV6 and *NTRK3* Gene Fusion Resulting in a Constitutively Active TRK Fusion Protein[5]

ATP, adenosine triphosphate; Ig, immunoglobulin; *NTRK*, neurotrophic tyrosine receptor kinase; SAM, sterile alpha motif; TRK, tropomyosin receptor kinase.

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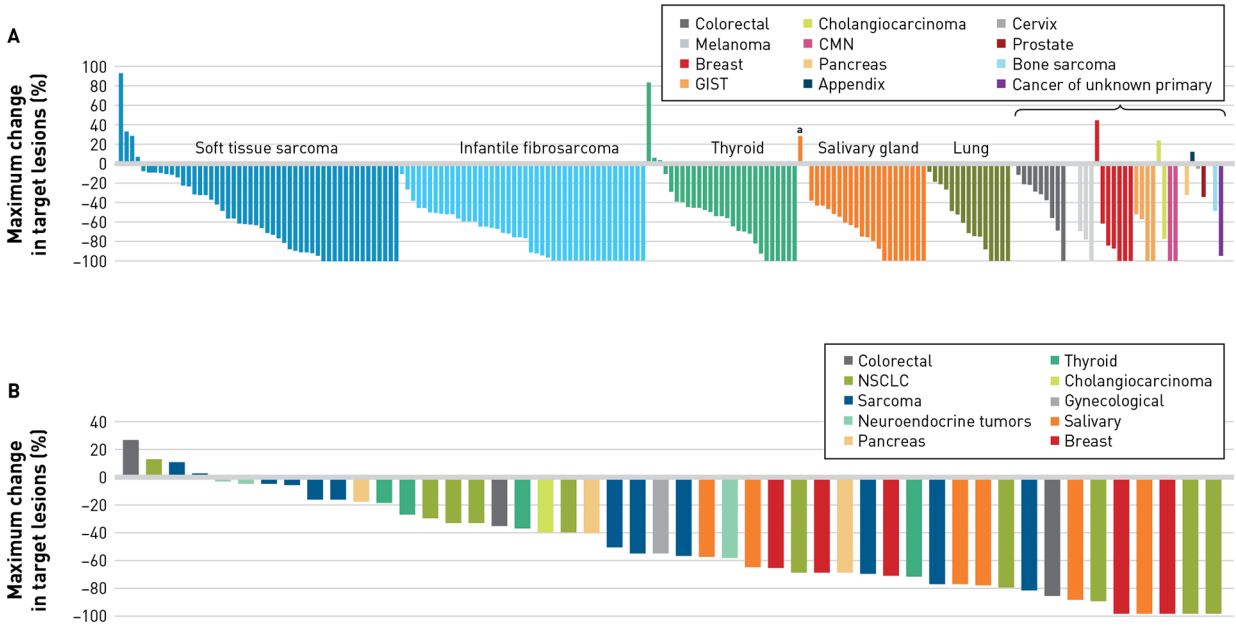

FIGURE 2.

Maximum Change in Target Lesions in Response to (A) Larotrectinib and (B) Entrectinib in Patients With TRK Fusion Cancer[35,41]

CMN, congenital mesoblastic nephroma; GIST, gastrointestinal stromal tumor; NSCLC, non–small cell lung cancer; TRK, tropomyosin receptor kinase.

[a]This patient had a TRK solvent front resistance mutation at baseline owing to previous therapy.

Figures reprinted with permission. (A) © 2021 American Society of Clinical Oncology. All Rights Reserved. Hong DS et al. ASCO annual meeting 2021, poster 3108. (B) Doebele RC et al. *Lancet Oncol*. 2020;21(2):271–282.

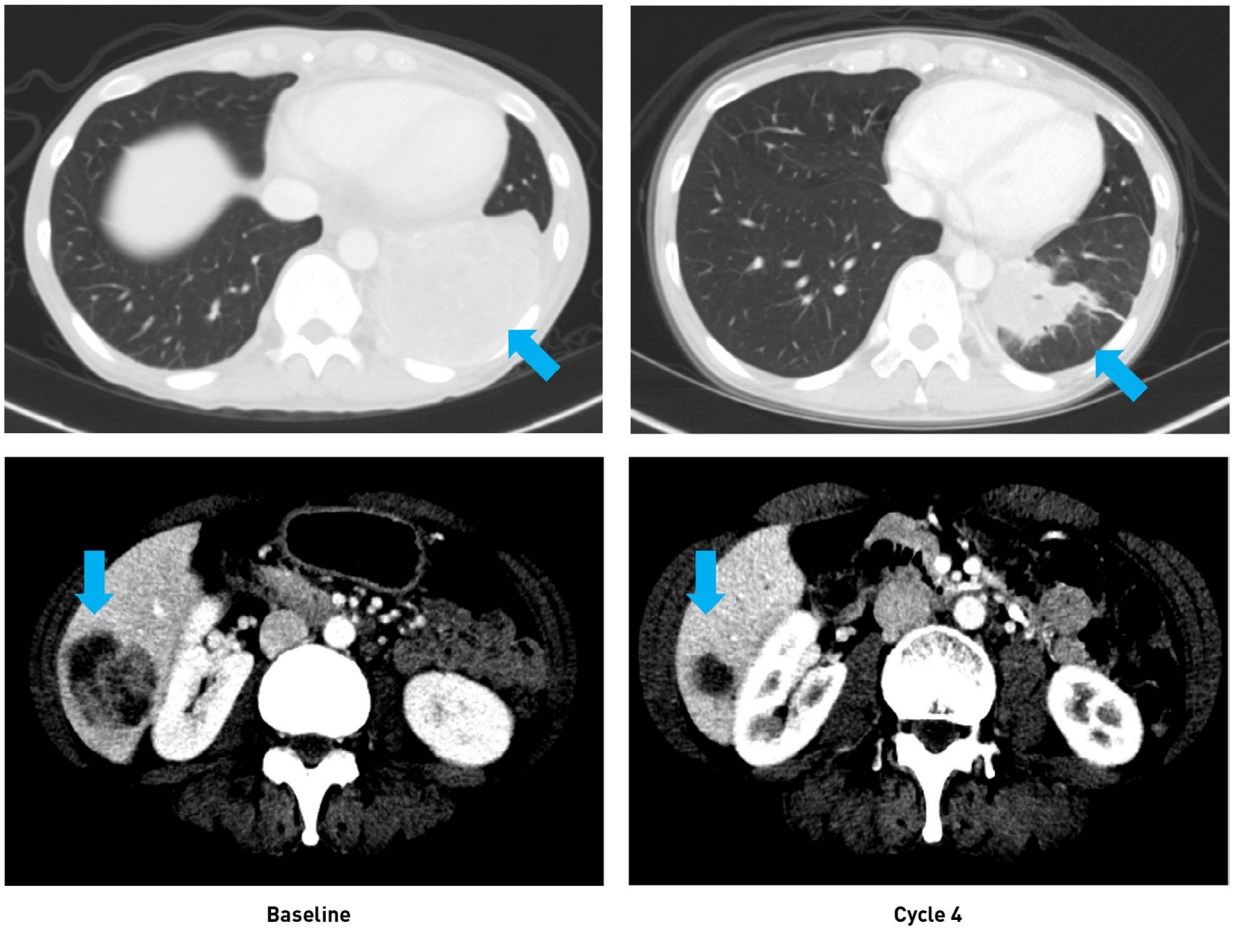

FIGURE 3.

Response to Larotrectinib in a Patient With Metastatic *SQSTM1-NTRK1* Non–Small Cell Lung Cancer[36]

A woman, aged 45 years, had *SQSTM1-NTRK1* non–small cell lung cancer with lung, liver, and mediastinal metastases. She had progressed following chemotherapy and developed pulmonary hypertrophic osteoarthropathy. She commenced larotrectinib 100 mg twice daily; within 1 week, she had joint pain relief and increased energy, and she had a partial response by cycle 4, with resolution of paraneoplastic symptoms. These clinical improvements corresponded to rapid and sustained improvements in patient-reported quality of life. After 15 months of treatment, the patient withdrew from the clinical trial following significant noncompliance.

Images courtesy of Shivaani Kummar, MD, FACP. Reproduced with permission from Kummar S et al. *Curr Probl Cancer*. 2021;45(6):100734.

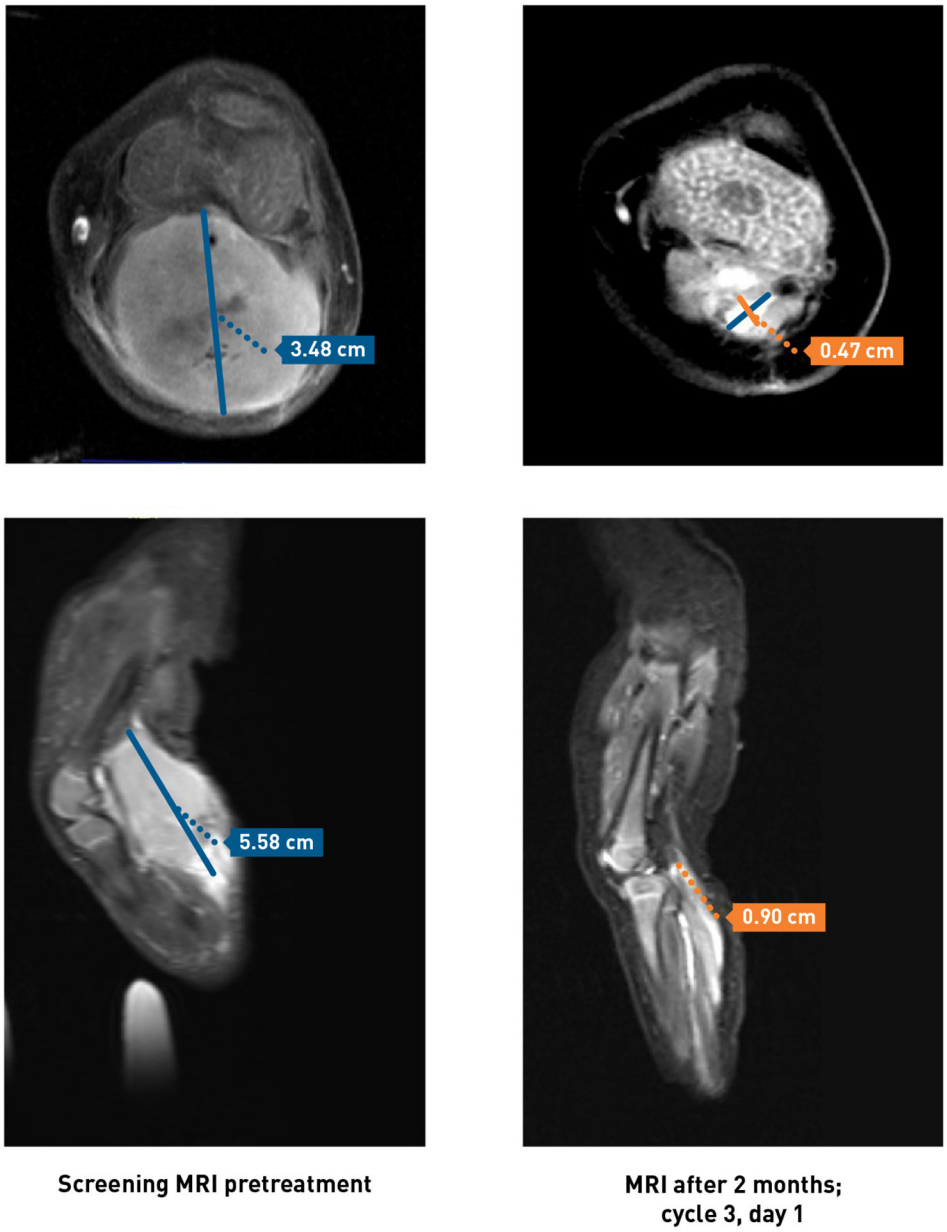

FIGURE 4.

Response to Larotrectinib in a Child With *ETV6-NTRK3* Infantile Fibrosarcoma

A boy, aged 1 month, had infantile fibrosarcoma in the left calf that harbored an *ETV6-NTRK3* gene fusion. The tumor was treatment naive and unresectable without potential major morbidity. The patient began larotrectinib 100 mg/m2 twice daily and had a rapid response after 2 cycles, with 91% tumor reduction. He was able to undergo surgical resection of the residual 0.5-cm mass when aged 8 months (cycle 6) and achieved a pathologic complete response. Treatment was discontinued at 2 months post resection. When aged nearly 4 years—35 months after discontinuing larotrectinib—the patient showed no evidence of disease. He was walking, running, and attending school, with normal neurocognitive development.

Images courtesy of Noah Federman, MD.

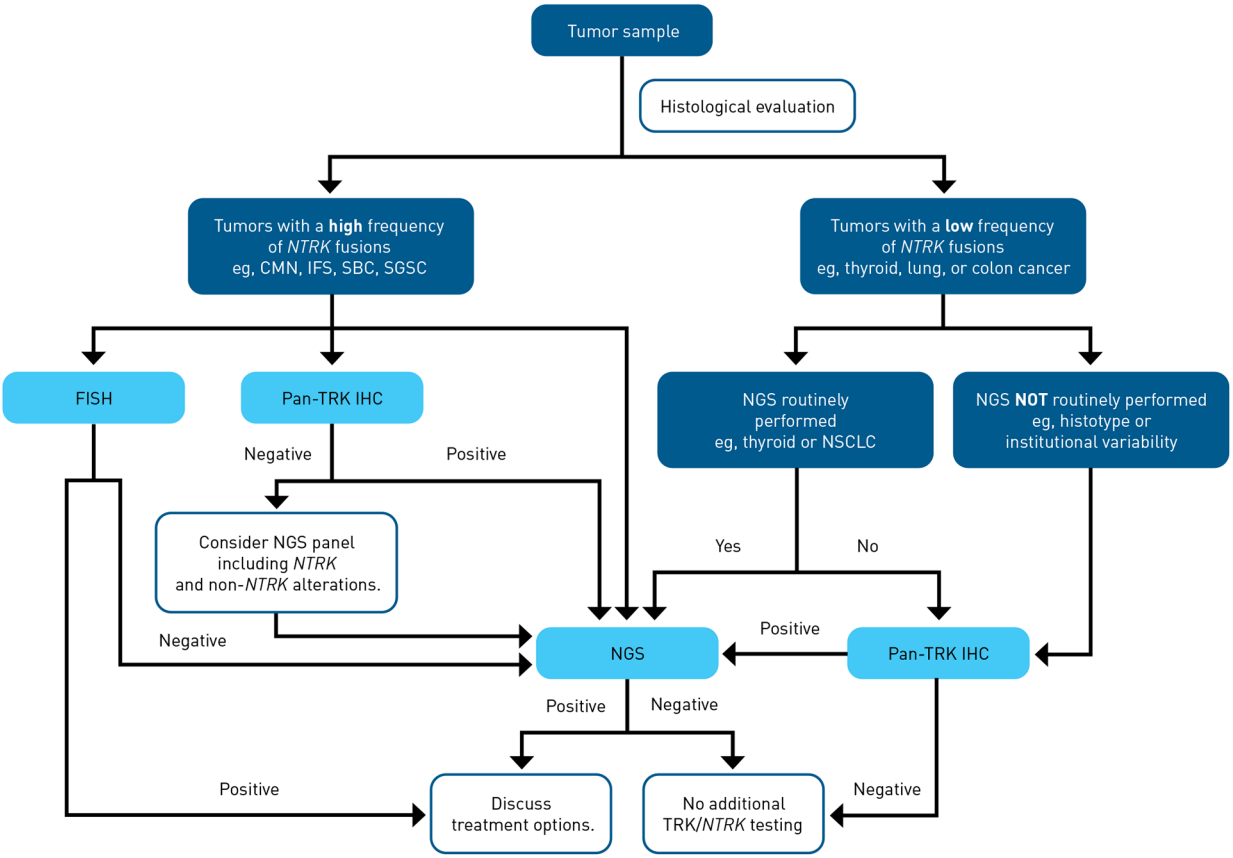

FIGURE 5.

NTRK Gene Fusion Testing Algorithm[5]

CMN, congenital mesoblastic nephroma; FISH, fluorescence in situ hybridization; IFS, infantile fibrosarcoma; IHC, immunohistochemistry; NGS, next-generation sequencing; NSCLC, non–small cell lung cancer; *NTRK*, neurotrophic tyrosine receptor kinase; SBC, secretory breast carcinoma; SGSC, salivary gland secretory carcinoma; TRK, tropomyosin receptor kinase.

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TABLE 1.

Overview of Testing Methods for *NTRK* Gene Fusions[5]

Assay	Advantages	Disadvantages
IHC	• Low cost • Readily available • Detects TRKA, B, and C • Turnaround time 1–2 days	• Not specific for *NTRK* gene fusions as it detects both wild-type and fusion proteins • Possible false positives • Possible false negatives for fusions involving TRKC • No standardization of scoring algorithms
FISH	• The location of the target within the cell is visible. • Several targets can be detected in 1 sample using several fluorophores. • Requires knowledge of only 1 of the 2 fusion partners when using break-apart probes • *NTRK* gene fusions with unknown partners can be detected using break-apart FISH. • FISH is readily available in most laboratories and institutes	• The target sequence must be known for conventional FISH; otherwise, 3 separate tests are required for *NTRK1*, *NTRK2*, and *NTRK3*. • Complex chromosomal translocations can result in false-positive signals. • False-negative results may be higher than 30%.
RT-PCR	• High sensitivity and specificity • Low cost per assay	• Target sequences must be known (ie, cannot readily detect novel fusion partners). • A comprehensive multiplex RT-PCR assay might be challenging because of the potentially large number of 5’ fusion partners.
NGS	• May detect novel fusion partners (depending on the assay used) • Can be used to evaluate multiple actionable targets simultaneously while preserving limited tissue • Currently used for *NTRK* testing • RNA-NGS is preferred over DNA- NGS because sequencing for RNA-based testing is focused on coding sequences, not introns.	• Commercially available DNA-based NGS platforms may not be capable of identifying all *NTRK* gene fusions, especially those involving *NTRK2* and *NTRK3*, which have large intronic regions. • DNA-NGS is limited by intron size. • RNA-NGS is limited by RNA quality.

FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; NGS, next-generation sequencing; *NTRK*, neurotrophic tyrosine receptor kinase; RT-PCR, reverse transcriptase polymerase chain reaction; TRK, tropomyosin receptor kinase.

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TABLE 2.

Frequency of *NTRK* Gene Fusions in Selected Tumor Types[16]

Histology	Frequency of *NTRK* gene fusions (%)	95% CI (%-%)
Secretory breast carcinoma	92.9	72.6–100
Fibrosarcoma, infantile (congenital)	90.6	67.4–100
Salivary gland secretory carcinoma	79.7	62.8–96.5
Pigmented spindle cell nevus of Reed	56.5	34.5–76.8
Pleomorphic adenoma	50.5	0.0–100
Papillary thyroid carcinoma, pediatric	26.0	11.1–46.3
Differentiated thyroid cancer, pediatric	22.2	6.4–47.6
Congenital mesoblastic nephroma (all subsets)	21.5	13.1–32.2
High-grade glioma	21.2	9.0–38.9
Low-grade mucoepidermoid carcinoma	20.0	5.7–43.7
Acinic cell carcinoma of salivary gland	11.1	4.2–22.6
Diffuse leptomeningeal glioneuronal tumor	10.0	2.1–26.5
Frequency of *NTRK* gene fusions in common tumor types		
Cervical carcinoma	0.4	0.0–0.8
Uterine soft tissue sarcoma	0.3	0.0–0.8
Cutaneous melanoma	0.3	0.1–0.6
Pancreatic adenocarcinoma	0.3	0.1–0.5
Colorectal adenocarcinoma	0.3	0.2–0.4
Neuroendocrine tumors	0.3	0.1–0.4
Non-small cell lung cancer	0.2	0.1–0.3
Invasive breast carcinoma	0.1	0.0–0.2
Examples of primary brain tumors		
High-grade glioma	21.2	9.0–38.9
Diffuse leptomeningeal glioneuronal tumor	10.0	2.1–26.5
High-grade glioma, pediatric	6.2	3.1–9.3
Glial, glioneuronal, and ependymal	3.3	0.4–11.4
Dysembryoplastic neuroepithelial tumors, pediatric	3.0	0.1–15.8
Low-grade glioma, pediatric	1.6	0.0–3.3
Glioma	1.0	0.0–2.8
Low-grade glioma	0.9	0.2–1.5
Glioma/neuroepithelial tumor	0.6	0.2–1.1

NTRK, neurotrophic tyrosine receptor kinase.

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TABLE 3.

Larotrectinib and Entrectinib Label Overview28,29,[a]

Attributes	Larotrectinib	Entrectinib
Indication	Adults and children	Adults and children 12 years and older
Dosing	100 mg twice a day for adults; 100 mg/m^2 twice a day (to a maximum of 100 mg per dose) for children	600 mg once a day for adults; 300 mg/m^2 once a day for children
Formulation	Capsules and liquid	Capsules
Response rate		
ORR	75%	57%
CR	22%	7.4%
PR	53%	50%
All-grade AEs in ≥ 20% of patients for either drug		
Fatigue	37%	48%
Dizziness	28%	38%
Nausea	29%	34%
Dyspnea	18%	30%
Myalgia	14%	28%
Increased weight	15%	25%
Arthralgia	14%	21%
Vision disorders	NR	21%
Cough	26%	24%
Vomiting	26%	24%
Constipation	23%	46%
Diarrhea	22%	35%
Dysgeusia	NR	44%
Edema	15%	40%
Dysesthesia	NR	34%
Cognitive impairment	NR	27%
Pyrexia	18%	21%
Warnings	Hepatotoxicity, embryo-fetal toxicity, neurotoxicity	Hepatotoxicity, embryo-fetal toxicity, CNS effects, congestive heart failure, skeletal fractures, hyperuricemia, QT interval prolongation, vision disorders
AE-related fatalities	None	Dyspnea (0.6%), pneumonia (0.6%), sepsis (0.6%), completed suicide (0.3%), large intestine perforation (0.3%), tumor lysis syndrome (0.3%)

AE, adverse event; CNS, central nervous system; CR, complete response; NR, not reported; ORR, objective response rate; PR, partial response.

[a]For illustrative purposes only; cross-trial comparisons must not be made.