Iran J Public Health, Vol. 54, No.4, Apr 2025, pp.710-722

Review Article

The Research Progress of Neurotrophic Tyrosine Receptor Kinase *(NTRK)* Gene Fusions and Tropomyosin Receptor Kinase (*TRK*) Inhibitors: A Narrative Review

Jielin Li, *Yuan Liang

Department of Thoracic Internal Medicine, Cancer Hospital of China Medical University, Liaoning Cancer Hospital & Institute, Shenyang 110042, Liaoning Province, China

***Corresponding Author:** Email: liangyuan@cancerhosp-ln-cmu.com

(Received 10 Sep 2024; accepted 16 Dec 2024)

Abstract

NTRK gene is responsible for encoding *TRK*, which consists of three family members: *NTRK1*, *NTRK2*, and *NTRK3*. These family members encode different proteins known as *TRKA*, *TRKB*, and *TRKC*, respectively. *NTRK* fusion genes are the clearest driving factor for carcinogenesis. *NTRK* gene fusion detection and *TRK* inhibitors are effective measures for the treatment of malignant tumors. The development of anti-tumor drugs targeting *TRK* proteins has been favored by various scientific research institutions and pharmaceutical companies. The first-generation *TRK* inhibitors, larotrectinib and entrectinib, have been approved for the treatment of pediatric and adult patients with metastatic or locally advanced solid tumors harboring *NTRK* fusion proteins, demonstrating remarkable anticancer efficacy in clinical settings. However, the issue of acquired resistance to *TRK* inhibitors has emerged. Currently, efforts are underway to develop next-generation *TRK* inhibitors based on sequence, structural, and kinetic methodologies, as well as to explore the intracellular signaling pathways of *TRK* and the mechanisms underlying resistance. The main focus of this review was to discuss the fusion of *NTRK* genes and the application of *TRK* inhibitor treatment.

Keywords: *NTRK* gene fusions; *Tropomyosin Receptor Kinase* (*TRK*) inhibitors

Introduction

As per the 2019 estimates WHO, cancer is presently among the primary reasons for global mortality (1). With the rapid development of genetic testing technology, research on driver genes and their targeted drugs has brought revolutionary changes to the treatment of advanced cancer. *Neurotrophic tyrosine receptor kinase* (*NTRK*) gene fusions have been proven to be the driving gene for multiple paediatric and adult cancer, including but not limited to thyroid cancer, lung cancer, breast cancer, colorectal cancer, and soft tissue sarcoma (2-3).

Several clinical trials (3-5) have demonstrated that *tropomyosin receptor kinase* (*TRK*) inhibitors have significant anti-tumor activity in solid tumors with *NTRK* gene fusions, with excellent safety profiles and controllable adverse reactions, bringing new hope to patients with advanced cancer.

This article presents a comprehensive review of the impact of *NTRK* gene fusions across various

DOI: 10.18502/ijph.v54i4.18410

tumour histologies, along with the treatments and resistance associated with *TRK* inhibitors.

Methods

To comprehensively collect research related to *NTRK* gene fusions and *TRK* inhibitors, we employed a narrative review retrieval strategy. The databases searched included PubMed, EMBASE, Web of Science, CNKI (China National Knowledge Infrastructure), WanFang, and VIP (Weipu), encompassing major scientific literature resources both internationally and within China. The time frame for the search was set from the establishment of the databases until Aug 2024, with language restrictions limited to Chinese and English. The combination of keywords utilized both Medical Subject Headings (MeSH) and free text terms to enhance the flexibility and breadth of the search. The specific retrieval strategy included: ("*NTRK*" OR "*Neurotrophic receptor tyrosine kinase*" OR "*tropomyosin receptor kinase*" OR "*TRK*") AND ("Malignant Neoplasm" OR "Cancer" OR "Tumor") AND ("*TRK* inhibitors"). We eliminated irrelevant literature by reading abstracts.

Ethics approval and consent to participate

As this study involves the summary and analysis of other studies, it does not involve medical ethics approval or patient-informed consent.

Functions of the NTRK Gene

The *NTRK* gene enables a variety of functions, including the activity of GPI-anchored ephrin receptors, neurotrophic factor binding activity, and the binding activity of the p75 neurotrophin receptor. The *NTRK* gene is involved in the regulation of nervous system development as well as the modulation of programmed cell death. It operates upstream or internally in the cellular response to growth factor stimulation and protein autophosphorylation. The *NTRK* gene is a component of cellular architecture, encompassing dendrites, endosomes, and neuronal cell bodies. A schematic representation of the genomic structure of the *NTRK* gene is illustrated in Fig. 1.

The functional characteristics of proteins encoded by NTRK genes

The *NTRK* gene family consists of three members, namely *NTRK1*, *NTRK2*, and *NTRK3*. The *TRK* family proteins, namely *TRKA*, *TRKB*, and *TRKC*, are encoded by genes found in various segments of chromosomes 1q21-22, 9q22.1, and 15q25. These proteins are vital for controlling neuron growth, differentiation, and apoptosis in the central and peripheral nervous systems (4-10). *TRK* receptor is a neurotrophic factor, whereas *TRK* serves as a receptor for nerve growth factor. Different neurotrophic factors exhibit a high affinity for specific *TRK* receptors. *TRKA* can be bound by *nerve growth factor* (NGF), *TRKB* can be bound by *brain-derived neurotrophic factor* (*BDNF*) and *neurotrophin-4/5* (NT4/5), *TRKC* can specifically bind to n*eurotrophin-3* (*NT-3*), although it can also bind to *TRKA* and *TRKB* (5-6,8-11). *TRK*, a transmembrane receptor protein, contains a conserved homologous structure region that includes an extracellular domain responsible for ligand binding, a transmembrane region, and an intracellular kinase domain arranged in sequence from the N-terminal to the C-terminal (8-10,12,13). Binding of their respective ligands to *TRKA*, *TRKB*, and *TRKC* receptors induces receptor dimerization and phosphorylation. This triggers a series of events that initiates subsequent signaling pathways like the *RAS/MAPK/ERK* pathway, *PLC-γ* pathway, and *PI3K/AKT* pathway, ultimately impacting cellular proliferation, differentiation, metabolism, apoptosis, and various other biological processes (2,7-13).

NTRK gene fusions

NTRK fusion genes are the clearest driving factor for carcinogenesis (14). *NTRK* fusion genes occur between *NTRK1, NTRK2,* or *NTRK3* and another unrelated gene, representing a significant genomic alteration with oncogenic potential, in contrast to the less common oncogenic mechanisms such as *NTRK* mutations, splice variants, and TRK overexpression.

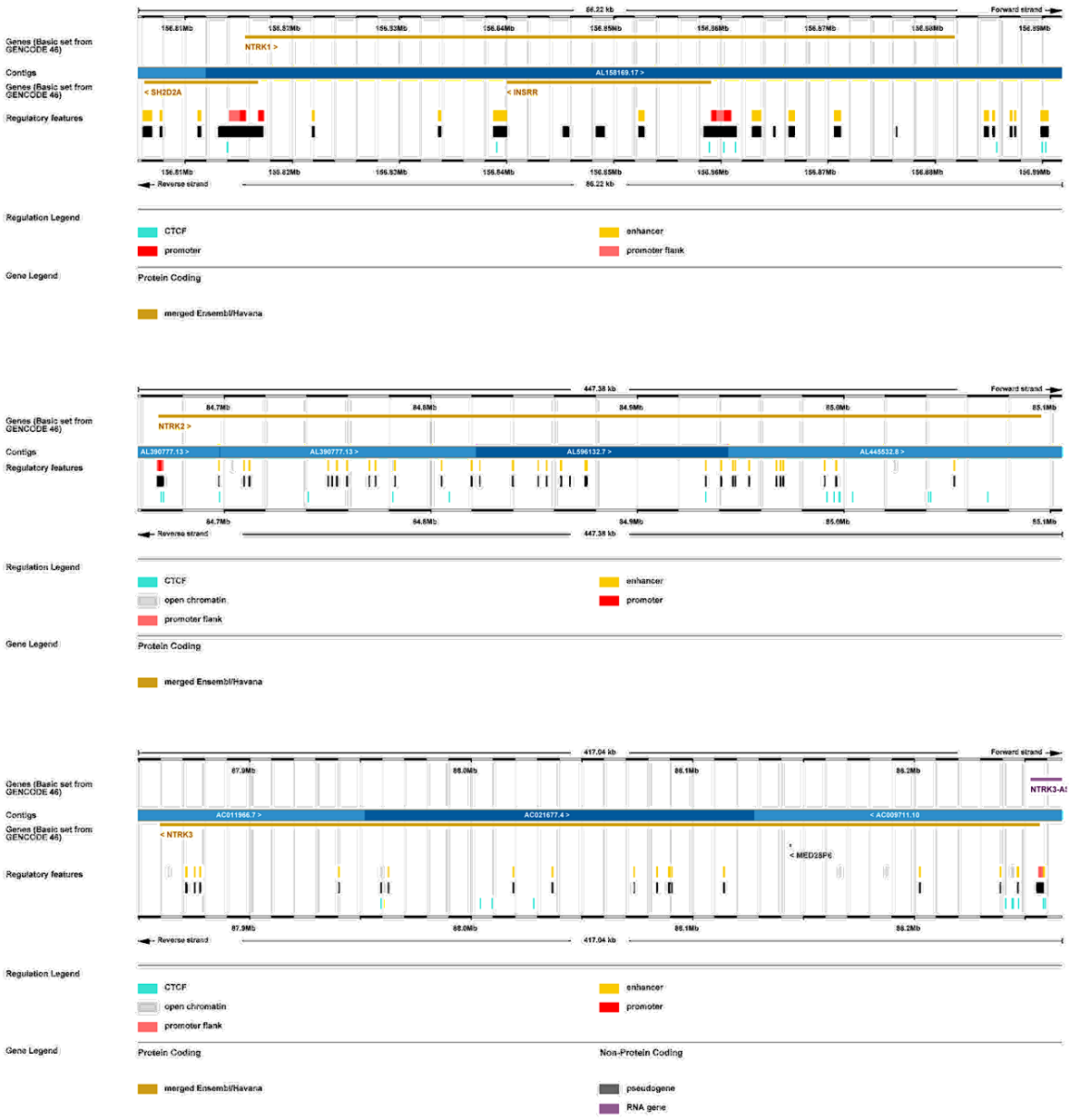

Fig. 1: The schematic view of genomic structure (*NTRK* gene). The picture are provided by Genetron Health Company

The oncogenic rearrangements of *NTRK* genes are typically caused by the fusion of the 3' region of the *NTRK* gene with the 5' region of an unrelated gene. *NTRK* fusion genes retain the kinase domain of the *TRK* receptor, while the 5' region gene sequence encodes one or more recognizable dimerization domains, resulting in the formation of a novel fusion protein through the in-frame fusion of the *TRK* receptor's kinase domain with the unrelated gene in the 5' region, a constitutively active *TRK* fusion protein, which serves as a true oncogenic driver. *TRK* fusion proteins can lead to ligand-independent dimerization, thereby activating the carboxy-terminal *TRK* kinase domain and driving downstream signaling pathways,

promoting cell survival and proliferation, and contributing to tumorigenesis (5,9,15).

The first discovery of *NTRK* gene fusion in colorectal cancer dates back to 1986 when the *TPM3-NTRK1* translocation was detected in tumor biopsy tissue (16). *NTRK* gene fusions exist in a variety of solid tumors, and their incidence varies depending on tumor types.Other genes that fuse with *NTRK* are called partner genes.More than eighty unique fusion partner genes have been identified up to now, of which the most common types are *ETV6-NTRK3*, *TPM3-NTRK1*, and *LMNA-NTRK1* (3,9).

Identifying *NTRK* gene fusions

At present, the primary techniques used to identify *NTRK* fusion genes are immunohistochemistry (IHC), fluorescence in situ hybridization (FISH), reverse transcription-polymerase chain reaction (RT-PCR), and next-generation sequencing (NGS). The current techniques for identifying *NTRK* gene fusions come with their individual constraints. Hence, the identification of *NTRK* gene fusions often employs a combined detection approach to ensure accurate gene status data (17,18).

IHC

IHC is employed to assess the protein expression levels in tumor cells and detect *NTRK* gene fusions (17). Currently, pan-Trk monoclonal antibodies are widely used for simultaneous detection of overexpression of *TRKA/B/C* proteins (18, 19). However, this method still has some limitations. Firstly, it is restricted to formalin-fixed paraffin-embedded (FFPE) tissue samples (18, 19). Secondly, the sensitivity and specificity vary in different tumors (20). Lastly, although immunohistochemistry can detect TRK proteins, it cannot differentiate between overexpression caused by fusion or amplification. IHC can serve as an alternative marker for *NTRK* gene fusions detection in routine screening, but it cannot be used as a companion diagnostic for treatment. Further validation through nucleic acid molecular-level testing is required for cases that are IHC positive (20).

FISH

FISH is a DNA-based highly sensitive detection method that utilizes separate or fused probes to detect gene fusions in cancers (21, 22). This detection method is inexpensive with a short turnaround time. Tissue embedded in paraffin can be used, and even with low tumor purity, the detection results are usually reliable (17).

RT-PCR

RT-PCR is a method used to detect fusion transcripts at the RNA level, requiring the design of primers for the adjacent exons upstream and downstream of the breakpoint. Thus, a prerequisite for this detection is the knowledge of the specific gene type of *NTRK*, the specific partner gene upstream, and the respective breakpoint of these two genes. In a study involving 25 MASC patients, standard RT-PCR was employed to detect the classic fusion transcript of exon 5 of the ETV6 gene with exon 15 of the NTRK3 gene, not detected in any cases (23).

Next-generation sequencing

A key benefit of DNA-based NGS is its capacity to concurrently evaluate various genetic alterations, including mutations, amplifications, deletions, and fusions, as well as assess microsatellite instability status and tumor mutation burden (21). However, for some genes with long intron sequences, such as *NTRK2* and *NTRK3*, it is difficult to fully cover all kinds of fusion mutations by DNA-based NGS due to the uncertainty of the fusion site (2,17-18,21). Furthermore, the turnaround time for DNA-based NGS typically takes at least two weeks (21).

RNA-based NGS involves extracting RNA from FFPE, followed by synthesing cDNA for sequencing (21). The primary benefits of this method include the definitive identification of active gene transcription and precise characterization of the specific genes and exons in the transcript. This approach overcomes the issue of intron coverage and offers more accurate detection. However, the disadvantage is that RNA samples are more unstable than DNA, and the requirements for samples are stringent (2,17,21,24).

Each technology has its advantages and limitations (Table 1). In the screening and confirmation process of *NTRK* gene fusions, in addition to the rational use of the aforementioned detection methods, the tumor type should also be considered.

Table 1: The advantages and limitations of *NTRK* gene fusion analysis methods

	IHC	FISH	RT-PCR	NGS
Sample requirements	FFPE tissue	FFPE tissue	FFPE, snap frozen, or stabilized tissue	FFPE, snap frozen, or stabilized tissue
Turnaround time	1-2 d	1-2 d	5-10 d	2-3 wk
Advantages	Rapid and inexpensive, widely available within clinical laboratories	Established approach, high sensitivity and specificity, requiring fewer samples, low tumor purity samples	Rapid and inexpensive, high sensitivity and specificity,gene fusion that can be detected at the RNA level	High sensitivity and specificity, highly scalable theoretically capable of detecting all classes of actionable mutations,including fusions with unknown partners
Disadvantages	Limited specificity, only be used as a preliminary screening for genetic testing	Requires expert Interpretation, does not confirm detected fusion is expressed	Design probes for known fusion, unable to detect fusion of multiple *NTRK* genes	Require high level of infrastructure Investment, requires high-level bioinformatics Capability, high cost, long detection cycle, adequate tumor purity is required

TRK inhibitors

Given that *NTRK* fusion genes serve as critical oncogenic drivers, promoting the growth and survival of cancer cells and potentially occurring in any part of the human body, the development of antitumor drugs targeting *TRK* proteins has garnered significant interest from various research institutions and pharmaceutical companies. In 2018 (25) , the world's first *TRK* inhibitor, larotrectinib, was approved for marketing in the United States, specifically for adult and pediatric patients with *NTRK* gene fusion-positive solid tumors. In 2019 (26) , entrectinib was also launched in the United States. Additionally, several targeted therapies aimed at *NTRK* gene fusions are currently in clinical trials, such as Repotrectinib and VC004, demonstrated promising research data. As the clinical application of TRK inhibitors becomes increasingly widespread, challenges in evaluating their efficacy have become more pronounced. Based on the differences in binding sites of small molecule inhibitors with TRK, they can be categorized into three types: Type I, Type II, and Type III. Type I kinase inhibitors target the adenosine triphosphate (ATP) binding site; Type II kinase inhibitors target both the ATP binding site and the adjacent hydrophobic pocket; Type III kinase inhibitors are also referred to as allosteric inhibitors. Information regarding the various generations of *TRK* inhibitors is presented in Table 2.

Table 2: Information on different generations of TRK inhibitors

Generation	Inhibitors	Type	Target	Indication
First	Larotrectinib	Type I	TRK	Advanced solid tumor, hematoma
First	Entrectinib	Type I	TRK, ALK, ROS1	Solid tumor, non-small cell lung cancer
Next	Selitrectinib	Type I	TRK	Solid tumor
Next	Repotrectinib	Type I	TRK, ALK, ROS1	Non-small cell lung cancer, solid tumor
Next	Taletrectinib	Type I	TRK, ROS1	Non-small cell lung cancer, solid tumor
Other	Merestinib	Type II	MET, MST1R, AXL, ROS1	Solid tumor
Other	Cabozantinib	Type II	TRK, MET, VEGFR1/2/3, ROS1, RET, AXL, KIT	Solid tumor, non-small cell lung cancer

First-generation TRK inhibitors

The broad-spectrum anticancer drugs Larotrectinib and Entrectinib, unrelated to tumor types, represent the first-generation tyrosine kinase inhibitors (TKIs) targeting the TRK protein. These medications competitively bind to the ATP-binding kinase domain, impeding the phosphorylation of tyrosine residues, thereby interrupting downstream pathways. Their role involves inhibiting the growth and proliferation of tumor cells mediated by *NTRK* fusion (27-30).

Larotrectinib

Developed by LOXO Oncology in collaboration with Bayer AG, Larotrectinib, previously called LOX-101, is a highly selective oral pan-TRK inhibitor targeting the TRK kinase family (28,31).

Clinical trials were conducted to evaluate the safety and effectiveness of Larotrectinib, which consisted of three trials: a phase I study (NCT02122913) involving adults (LOXO-TRK-14001), a phase I study (NCT02637687) involving children (SCOUT), and a phase II study (NCT02576431) involving adolescents and adults (NAVIGATE) (32). A combined number of 55 individuals diagnosed with *NTRK* fusion-positive were included in the study, among whom 12 were children. Based on an evaluation conducted by an impartial reviewer, the Objective Response Rate (ORR) stood at 75%, while as per the investigator's assessment, it reached 80%. Larotrectinib was well tolerated, and there were no patients who had to stop treatment due to drug-related side effects.

At the point of larotrectinib's market approval, the median duration of its therapeutic response and progression-free survival (PFS) had yet to be determined. To clarify the above problems, the phase I/II clinical trials of larotrectinib (NCT02122913, NCT02576431, NCT02637687) were analyzed (33). In the study, 159 patients were enrolled, of whom 153 were eligible for evaluation,the ORR was 79%. Among 102 adult patients, ORR was 73% and among 51 pediatric patients, ORR was 92%. The median duration of response (DOR) was 35.2 months, the median PFS stood at 28.3 months, while the median overall survival (OS) reached 44.4 months. There were 12 patients with brain metastases in the study, of which 9 were effective, ORR was 75%, which was very close to 79% of the overall population, indicating that larotrectinib also had an excellent effect on central nervous system metastasis. The most frequently observed grade 1 or 2 adverse events included tiredness, cough, constipation, and elevated levels of alanine aminotransferase (ALT) or aspartate aminotransferase (AST). Larotrectinib has shown remarkable effectiveness in maintaining disease control in patients with *NTRK* fusion-positive tumors. Additionally, it is well-tolerated and significantly improves the quality of life for patients (34).

Entrectinib

Entrectinib, previously identified as RXRD-101 and NMS-E628, is an orally administered selective inhibitor targeting TRK, ROS1, and ALK, designed by Roche. This substance exhibits significant activity in the central nervous system (CNS) and is employed to treat different solid tumors that have *NTRK1/2/3* or ROS1 gene fusions. The high ability of this medication to pass through the blood-brain barrier is a distinguishing feature (29,35).

The safety and effectiveness of entrectinib were evaluated in a combined analysis of three clinical trials: STARTRK-1 (NCT02097810), ALKA-372-001 (EudraCT, 2012-000148-88), and STARTRK-2 (NCT02568267), which included Phase I and Phase II studies. Entrectinib was administered to 54 patients advanced or metastatic solid tumors with *NTRK* fusion. The ORR was 57.4%, with a complete response rate of 7.4%. The median DOR was 10.4 months, while the median PFS and OS were 11.2 months and 20.9 months, respectively. Out of the patients who had CNS metastases at the beginning, 54.5% showed a positive response within the brain, and 27.3% experienced a complete respons (36,37).

A Phase I/IB clinical trial of entrectinib (STARTRK-NG, NCT02650401) was a dose escalation and expansion study in both children and adolescents (38). Among the 6 CNS tumors, there was 1 case that attained a CR, 3 cases that achieved a PR, 1 case with an unconfirmed PR, and 1 case that is still pending evaluation. Out of the 8 extracranial solid tumors, 6 exhibited a fusion, with 1 of them attaining a C, while 5 achieved a PR.The response of Entrectinib to solid tumors and CNS tumors with *NTRK1/2/3*, ROS1, and ALK fusions is notable, quick, and enduring.

Entrectinib previously induced deep (ORR 57.4%) and durable (DoR 10.4m) responses in adults with NTRK fusion-positive solid tumors from I/II trials. At clinical cut-off (August 31, 2020) (39), the efficacy evaluable population comprised 121 adults, the median survival follow-up time was 25.8 months, median DoR was 20.0 months, median PFS was 13.8 months. In 11 patients with blinded independent central review (BICR) -assessed measurable CNS disease, intracranial ORR was 63.6% and median intracranial DoR was 22.1 months. The most common adverse events reported were grade 1-2, including dysgeusia, diarrhea, fatigue, weight increase, etc. With additional clinical experience, entrectinib continues to demonstrate durable systemic and intracranial responses.

Next-generation TRK inhibitors

Patients might encounter problems with resistance when using first-generation TRK inhibitors, classified as either target resistance or off-target resistance. Target resistance mainly involves *NTRK1*/*NTRK3* (40).

The primary mechanism for target resistance is mutations in the *TRK* kinase domain. Resistance to *TRK* inhibitors is caused by these mutations, which disrupt inhibitor binding, change the conformation of the kinase domain, or affect ATP binding affinity, leading to resistance against *TRK* inhibitors (40). The occurrence of structural domain mutations is similar to mutations in ALK and ROS-1 kinases (40, 41). These mutations lead to the substitution of amino acids in three major regions: solvent-front mutations, gatekeeper site mutations, and xDFG-motif structural sequence.

The mechanism of off-target resistance is primarily associated with genetic alterations in other receptor tyrosine kinases or downstream pathway drivers of *TRK*. Similar to *ALK* and *ROS-1* fusion-positive lung cancer (31,40), *TRK* fusion-positive lung cancer can develop off-target resistance to *TRK* inhibitor therapy. *KRAS* mutations, *MET* amplification, *BRAFV600E* mutations, and activation of *IGF1R* have been identified in tumors and/or plasma samples of *TRK* inhibitor-resistant patients, suggesting a potential association with resistance development (42). The efficacy of drug combinations involving *TRK* and related kinase inhibitors in combating resistance requires further exploration.

The emergence of the second-generation TRK inhibitors, Selitrectinib (LOXO-195), Repotrectinib (TPX-0005) and Taletrectinib (DS-6051b/AB-106), aims to the resistance issue.

They are designed as low-molecular-weight macrocyclic structures to accommodate large side chains of alternative amino acids, thereby avoiding spatial collisions.

Selitrectinib (LOXO-195)

Selitrectinib (LOXO-195), a novel orally administered next-generation TRK inhibitor,a collaboration between LOXO Oncology and Bayer AG, exhibits robust efficacy against secondary resistance mutations in the TRK kinase domain. This is supported by results from enzyme and cell-based assays, as well as in vivo tumor models(43, 44).

Repotrectinib (TPX-0005)

Repotrectinib (TPX-0005) is a new oral next-generation multi-target drug with formidable activity and high selectivity that was developed by Turning Point Therapeutics in United States, which can inhibit ALK, ROS1, and *NTRK*, and had been obtained Orphan Drug Designation from the U.S. FDA in 2017(42,45). Patients with ALK, ROS1, or *NTRK* gene rearrangements or fusions, inevitably develop resistance after TKIs treatment. New mutations can arise as a resistance mechanism, such as the frequently observed ALK G1202R mutation following treatment with alectinib or ceritinib in ALK-rearranged cancers (46); ROS1 G2032R and ROS1 D2033N may develop following crizotinib therapy in ROS1-fusion tumors (47,48); NTRK1 G595R and NTRK3 G623R can appear after treatment with entrectinib or Larotrectinib in *NTRK*-rearranged cancers (32, 40, 41). Based on the preclinical data, repotrectinib exhibited a strong responsiveness to fusion genes containing solvent-front mutations (*NTRK1* G595R, *NTRK3* G623R, *ALK* G1202R, *ROS1* G2032R/D2033N) both in laboratory tests and in live subjects (42).

During the 2023 ESMO conference, the most recent safety and effectiveness information regarding repotrectinib (TRIDENT-1) for treating individuals with *NTRK*-positive was disclosed (data collected until Dec 19, 2022) (49). Out of a cohort of 40 patients diagnosed with untreated *NTRK*-positive advanced solid tumors, monitored for an average duration of 17.8 months, the ORR was found to be 58%. The intracranial objective response rate of measurable brain metastasis patients was 100%. Among the group of 48 individuals diagnosed with *NTRK*-positive advanced solid cancers, previously undergone *TKI* therapy, and were monitored for an average duration of 20.1 months, the ORR was recorded at 50%. Notably, patients with detectable brain metastases exhibited a remarkable intracranial ORR of 100%. The majority of adverse events were of grade 1-2, and the commonly reported ones included dizziness, fatigue, constipation, dysgeusia, and dyspnea. Irrespective of prior utilization of *TKIs*, patients with *NTRK* fusion-positive solid tumors demonstrated improved response rate and tolerability when treated with repotrectinib.

Taletrectinib (DS-6051b/AB-106)

Taletrectinib (DS-6051b/AB-106) is a new generation of *ROS1* and *NTRK* target small molecule tyrosine kinase inhibitor with high efficiency, high selectivity, and crossing blood-brain barrier developed by Daiichi Sankyo and AnHeart. The experiments confirmed that taletrectinib had a strong anti-tumor effect on *ROS1*/*NTRK* gene fusions (50).

In May 2018, the results of the Phase I clinical study of DS-6051b in Japan (NCT02675491) were published in Oncotarget (51). In this study, 15 participants diagnosed with NSCLC and having ROS1 fusion-positive were included, 12 were evaluable, the ORR was 58.3%. Regrettably, the study did not involve any individuals with *NTRK* fusion-positive solid tumors.

In June 2020, Clinical Cancer Research published the findings from the Phase I clinical trial (NCT02279433) conducted in the United States (52). Overall, 46 patients with solid tumors were enrolled, *ROS1* fusions (9 cases), *NTRK* fusions (3 cases), and other gene mutations (34 cases). Out of the 6 evaluable patients with *ROS1*+NSCLC who were resistant to crizotinib, the ORR was 33.3%, and the PFS was 4.1 months. In a patient with thyroid papillary carcinoma, the presence of the *TPM3-NTRK1* gene

fusion was identified following thyroidectomy, chemoradiation, radioactive I-131, sorafenib, and *PD-1* treatment. Subsequently, taletrectinib was administered, resulting in a DOR of 33.4 months (as of September 2019, the most recent tumor assessment time). Initial confirmation indicated that taletrectinib exhibited efficacy against ROS1 NSCLC and *NTRK* fusion-positive solid tumors.

Other TRK inhibitors

Merestinib (LY2801653)

LY2801653, also known as Merestinib, is a small molecule inhibitor of tyrosine kinases that can be taken orally. Preclinical studies have demonstrated effectiveness in blocking various tyrosine oncokinases, such as *MET, MST1R, AXL, MERTK, MKNK1/2, ROS1, and NTRK1/2/3* (53,54). Merestinib, identified as a type II NTRK1 kinase inhibitor based on x-ray crystallography investigations, has exhibited in vivo efficacy against cancer models harboring *TPM3-NTRK1* or *ETV6-NTRK3* gene fusions. Furthermore, it has effectively retained its strength in both laboratory and living organisms, specifically in *NIH-3T3* cells that have been altered to exhibit *TPM3-NTRK1* along with a G667C mutation in the kinase region (54).

Cabozantinib

Exelixis developed Cabozantinib, a small molecule tyrosine kinase inhibitor that targets multiple sites. Cabozantinib can strongly inhibit *VEGFR* and *MET* and is also active against *RET, AXL, KIT, TIE-2, FLT-3, ROS-1,* and *NTRK* (55,56). The dysregulation of signal pathways mediated by these targets is often associated with tumor occurrence, proliferation and metastasis, tumor angiogenesis, and maintenance of the tumor environment. By inhibiting them, downstream signal transduction can be prevented and tumor cell apoptosis can be caused (55). An in vivo study revealed that *NTRK* G595R mutation was highly resistant to entrectinib, larotrectinib, and cabozantinib, in contrast, *NTRK* G667C mutation was highly resistant to entrectinib and larotrectinib but sensitive to cabozantinib (57).

In addition, some other TRK inhibitors, such as Belizatinib (TSR-011), Sitravatinib (MGCD516), PLX7486, TL118, ICP-723, FCN-011, FCN-098 and so on, are currently in different stages of clinical trials (Table 3).

Table 3: Open clinical trials recruiting patients with *NTRK* alterations

Drugs	Phase	Official Title	NCTID
Larotrectinib	Phase 1	A Phase 1 Study of the Oral TRK Inhibitor Larotrectinib in Adult Patients with Solid Tumors	NCT02122913
Larotrectinib	Phase 1/2	A Phase 1/2 Study of the Oral TRK Inhibitor Larotrectinib in Pediatric Patients with Advanced Solid or Primary Central Nervous System Tumors	NCT02637687
Larotrectinib	Phase 2	A Study to Learn How Well the Drug Larotrectinib Works in Adults With Different Solid Cancers With a Change in the Genes Called NTRK Fusion	NCT02576431
Entrectinib	Phase 1	A Phase 1, Multicenter, Open-Label Study of Oral Entrectinib (RXDX-101) in Adult Patients with Locally Advanced or Metastatic Cancer Confirmed to be Positive for NTRK1, NTRK2, NTRK3, ROS1, or ALK Molecular Alterations	NCT02097810
Entrectinib	Phase 2	An Open-Label, Multicenter, Global Phase 2 Basket Study of Entrectinib for the Treatment of Patients with Locally Advanced or Metastatic Solid Tumors That Harbor NTRK1/2/3, ROS1, or ALK Gene Rearrangements	NCT02568267
Entrectinib	Phase 1/1b	A Phase 1/2, Open-Label, Dose-Escalation and Expansion Study Of Entrectinib (Rxdx-101) In Pediatrics With Locally Advanced Or Metastatic Solid Or Primary CNS Tumors And/Or Who Have No Satisfactory Treatment Options	NCT02650401
Selitrectinib	Phase 1	Expanded Access to Provide Selitrectinib (BAY2731954) for the Treatment of Cancers With a NTRK Gene Fusion.	NCT03206931
Selitrectinib	Phase 1	A Phase 1 Study of the TRK Inhibitor Selitrectinib (BAY 2731954) in Adult and Pediatric Subjects with Previously Treated *NTRK* Fusion Cancers	NCT03215511
Repotrectinib	Phase 1/2	A Phase 1/2, Open-Label, Multi-Center, First-in-Human Study of the Safety, Tolerability, Pharmacokinetics, and Anti-Tumor Activity of TPX-0005 in Patients With Advanced Solid Tumors Harboring ALK, ROS1, or NTRK1-3 Rearrangements (TRIDENT-1)	NCT03093116
Repotrectinib	Phase 1/2	A Phase 1/2, Open-Label, Safety, Tolerability, Pharmacokinetics, and Anti-Tumor Activity Study of Repotrectinib in Pediatric and Young Adult Subjects With Advanced or Metastatic Malignancies Harboring ALK, ROS1, NTRK1-3 Alterations	NCT04094610

Table 3: Continued …

Repotrectinib	Phase 3	Randomized, Open-label, Multicenter, Phase 3 Trial of Repotrectinib Versus Crizotinib in Participants With Locally Advanced or Metastatic Tyrosine Kinase Inhibitor (TKI)-naïve ROS1-positive Non-Small Cell Lung Cancer (NSCLC) (TRIDENT-3)	NCT06140836
Taletrectinib(DS-6051b）	Phase 1	Phase 1 Study of DS-6051b in Japanese Subjects With Advanced Solid Malignant Tumors Harboring Either a ROS1 or *NTRK* Fusion Gene	NCT02675491
Taletrectinib(DS-6051b)	Phase 1	A Phase 1/1B Multi-Center, Non Randomized, Open-Label, Multiple Dose First-In-Human Study Of DS-6051b, An Oral ROS1 And NTRK Inhibitor, In Subjects With Metastatic and/or Unresectable Solid Tumors	NCT02279433
Taletrectinib(DS-6051b）	Phase 2	A Multicenter, Open Label, Single Arm Phase 2 Study of AB-106 in the Treatment of Locally Advanced and Metastatic NSCLC	NCT04395677
Merestinib	Phase 2	A Phase II Study of Merestinib in Non-Small Cell Lung Cancers Harboring MET Exon 14 Mutations and Solid Tumors With NTRK Rearrangements	NCT02920996
Cabozantinib	Phase 2	A Phase II Study of Cabozantinib in Patients With RET Fusion-Positive Advanced Non-Small Cell Lung Cancer and Those With Other Genotypes: ROS1 or *NTRK* Fusions or Increased MET or AXL Activity	NCT01639508
Belizatinib (TSR-011)	Phase 1/2	A Phase I/IIa Open-Label, Dose Escalation and Cohort Expansion Trial of Oral TSR-011 in Patients With Advanced Solid Tumors and Lymphomas	NCT02048488
Sitravatinib(MGCD516)	Phase 1	A Phase 1/1b Study of MGCD516 in Patients With Advanced Solid Tumor Malignancies	NCT02219711
PLX7486	Phase 1	A Phase 1 Study to Assess Safety, Pharmacokinetics, and Pharmacodynamics of PLX7486 as a Single Agent in Patients With Advanced Solid Tumors	NCT01804530
TL118	Phase 2	A Phase 2 Study of TL118 for the Treatment of Patients With Solid Tumors Harboring *NTRK* Gene Fusions	NCT06010342
ICP-723	Phase 1/2	A Multi-center, Non-Randomized, Open-Label Phase 2 Basket Clinical Trial to Evaluate ICP-723 in Patients With Advanced Solid Tumors or Primary Central Nervous System Tumors	NCT05745623
FCN-011	Phase 2	A Multicenter, Open, Single-arm Phase I Dose Exploration and Phase II Extended Study Was Conducted to Evaluate the Safety, Tolerability, Pharmacokinetic Characteristics, and Primary Antitumor Activity of FCN-011 in Patients With Advanced Solid Tumor (Phase I) and *NTRK* Fusion Positive Advanced Solid Tumor (Phase II)A Multicenter, Open, Single-arm Phase I Dose Exploration and Phase II Extended Study Was Conducted to Evaluate the Safety, Tolerability, Pharmacokinetic Characteristics, and Primary Antitumor Activity of FCN-011 in Patients With Advanced Solid Tumor (Phase I) and *NTRK* Fusion Positive Advanced Solid Tumor (Phase II)	NCT04687423
FCN-098	Phase 1	A Multi-center, Open, Single-arm Phase I Dose Exploratory Study to Evaluate the Safety, Tolerability, Pharmacokinetic Properties and Primary Antitumor Activity of FCN-098 in Patients With Advanced Solid Tumors	NCT05212987

Conclusion

NTRK gene fusions function as the causative gene for numerous solid tumors in both children and adults. These fusions can currently be identified through IHC, FISH, RT-PCR, or NGS techniques. Larotrectinib or entrectinib, which are *TRK* inhibitors of the first-generation, have shown remarkable effectiveness against solid tumors with *NTRK* fusion and have proven to be safe and well-tolerated by patients. Despite the ongoing challenge of acquired resistance, the next-generation *TRK* inhibitors have the ability to overcome resistance caused by mutations in the *NTRK* kinase domain. As scientific advancements continue, *TRK* inhibitors will offer fresh prospects for patients with solid tumors that have *NTRK* fusion positivity.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

Funding

Not applicable.

Conflicts of Interest

The author has no conflicts of interest to declare.

Data availability statement

The data used to support the findings of this study are included within the article.

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