Review Article

NTRK1/2/3: biology, detection and therapy

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Abstract: The tropomyosin receptor kinase (TRK) receptor family comprises 3 transmembrane proteins named TrkA, TrkB, and TrkC, which are encoded by the *NTRK1*, *NTRK2*, and *NTRK3* genes, respectively. These tyrosine kinase receptors are physiologically expressed in human neuronal tissue and play essential roles in nervous system development and function. Gene fusions involving *NTRK* genes lead to transcription of constitutively active TRK proteins and drive oncogenesis in a broad range of different tumor types, including lung cancer. *NTRK* gene fusions represent an infrequent molecular alteration: in non-small cell lung cancer (NSCLC) they have been found in 0.1–0.2% of cases. However, these genetic alterations have recently become the subject of clinical interest as therapeutic targets. Because of the rarity of *NTRK* gene fusions in solid tumors and the complexity of fusion patterns, detection of these molecular alterations is complicated. However, screening cancer patients for *NTRK* fusions is critical in the clinical practice of precision cancer medicine, given the important therapeutic options currently available. There are several methods of detection, including immunohistochemistry, fluorescence in situ hybridization, reverse transcription polymerase chain reaction, and next-generation sequencing (DNA- and/or RNA-based), each of which has pros and cons. Major regulatory agencies provide recommendations on the optimal ways to detect *NTRK* fusions and the prescription of related targeted drugs, but these are subject to heterogeneity around the world. The first generation of selective TRK inhibitors, larotrectinib and entrectinib, have been studied in phase 1/2 clinical trials in adult and pediatric solid tumors, and results have demonstrated high and durable response rates and generally good tolerability. The approval of larotrectinib and entrectinib by U.S. and European regulatory agents for any *NTRK* fusion-positive cancer was a major breakthrough in precision medicine. This review aims to describe the prevalence and role of *NTRK* fusions in the biology of NSCLC and to summarize the detection methods and available treatment data.

Keywords: Neurotrophic tropomyosin receptor kinase (NTRK); non-small cell lung cancer (NSCLC); agnostic; larotrectinib; entrectinib

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Introduction

Background

The use of genetics and molecular biology to target different types of cancer is one of the most important innovations of the last decade in the cancer treatment landscape. Among these important advances, one of the most promising is the "tissue agnostic" approach of basing cancer treatment not on the histology or origin of the primary tumor, but on its genetic and molecular characteristics. Drugs classified as tumor-agnostic are molecules approved for the treatment of various types of cancer, regardless of the organ or tissue

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of origin, that target specific gene or protein alterations. This new approach has revolutionized cancer treatments, offering personalized treatment options based on the molecular characteristics of the disease. The first agnostic indication by the Food and Drug Administration (FDA) came in May 2017 with the approval of pembrolizumab, a programmed death 1 inhibitor, for adult and pediatric patients affected by unresectable or metastatic solid tumors with high microsatellite instability or mismatch-repair deficiency (MSI-H or dMMR), based on the results of the Keynote-158 study (1). Among the molecular alterations that have contributed most to changing the therapeutic landscape of cancer diseases are gene fusions of the neurotrophic tropomyosin receptor kinase (*NTRK*) (2).

These membrane-bound receptors have an important pathogenetic role for different cancers when altered and have become an important therapeutic target in recent years.

Rationale and knowledge gap

Because of the rarity of *NTRK* gene fusions in solid tumors and the technical problems associated with the complexity of fusion models, detection of molecular alterations in the *NTRK* gene is complicated but critical in the clinical practice of precision cancer medicine. Different detection methods, including immunohistochemistry, fluorescence *in situ* hybridization, reverse transcription polymerase chain reaction, and next-generation sequencing (NGS) (DNA- and/or RNA-based), have pros and cons that will be discussed in the following sections. There are also global regulatory issues on the optimal ways of detecting *NTRK* fusions and prescribing related targeted drugs, for which the FDA, the European Medicines Agency (EMA), and expert consensus are trying to provide a solution. Despite the promising results of therapeutic inhibition of *NTRK*, histologic-agnostic drug development efforts seek to make sure that patients who receive therapeutic agents targeting a driver mutation can benefit from treatment, considering the type of *NTRK* fusion partner, coexisting mutations, and resistance pathways known to date.

Objective

This review aims to provide a detailed and comprehensive description of the biological role of *NTRK* fusions, their prevalence in solid tumors and particularly in non-small cell lung cancer (NSCLC), methods of screening and detection of these rare molecular alterations, and recent scientific advances in the targeted treatment of *NTRK*-positive patients.

Unlocking the potential of *NTRK* in solid tumors and NSCLC: biology, detection, and precision targeted therapies

Biology

Physiological role of TRK genes and receptors

The Trk family of tyrosine-protein kinases (TrkA, TrkB, and TrkC) are the signaling receptors that mediate the biological properties of the nerve growth factor (NGF) family of neurotrophins (3). NGF is the usual agonist of the TrkA receptor. TrkB can bind both brain-derived neurotrophic factor (BDNF) and neurotrophin-4 (NT-4). TrkC is the primary receptor for neurotrophin-3 (NT-3) (3). TrkA is an NGF-activated receptor that undergoes dimerization and autophosphorylation, triggering several intracellular signaling pathways such as the PI3K (phosphatidylinositol 3-kinases), the Akt protein kinase pathway, and the Ras-MAP kinase signaling cascade (4). It also causes the release of intracytoplasmic Ca2+ and the activation of the intracellular inositol 1,4,5-trisphosphate receptors. When the TrkA signaling is activated by NGF, pro-apoptotic pathways are suppressed while the prosurvival pathways are activated; physiologically this leads to protection for neurons from death resulting from various insults, including axotomy, ischemia, oxidative stress, and glutamate receptor-mediated excitotoxicity (5). Another binding partner for this receptor is NT-3, which activates TrkA by a different molecular mechanism than that mediating NGF/TrkA signaling and seems to play a role in driving local axonal growth (4). TrkB has been shown to be crucial for the progression of neural kindling, and its role in epilepsies has recently been emphasized. TrkB's natural binding companion is BDNF, which is found in high concentrations in brain areas associated with seizure susceptibility (6). TrkC is activated by NT-3-induced dimerization, leading to a rapid generation of phosphorylated docking sites for adaptor cytoplasmic proteins, such as proteins containing phosphotyrosine-binding and/or Src homology 2 domains (SH2), and translating the sensory fiber projections into the ventral horn (4).

The interaction and affinity of each receptor can be modified due to alternative splicing of the protein, which produces genetic variants affecting its biological function. TrkA has three described isoforms that are expressed both in neuronal and non-neuronal tissues (TrkAI, TrkAII, and

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TrkAIII). The TrkAIII isoform, originally identified in neuroblastoma, is normally expressed by neural stem cells (7). A kinase-intact isoform and a truncated isoform of the TrkB protein (TrK-T-TK) have also been described. TrkC isoforms have no functional alteration and can be activated by NT-3 have also been reported. Isoforms lacking the kinase domains of TrkB and TrkC were described in a study by Brodeur *et al.* in neuroblastomas (8).

NTRK gene rearrangements in cancer: fusion partners and prevalence

The permanent activation of the Trk receptors can occur through chromosomal inversions and deletions, but the most common alterations of *NTRK* associated with cancer are gene fusions. *NTRK* gene rearrangements are translocations involving the three prime untranslated region (3'UTR) of the gene joining the five prime untranslated region (5'UTR) of a fusion partner gene (9). The fusion product is a chimeric protein that has constitutive, ligand-independent activation of the Trk kinase. This activation is expressed through the binding of TRK oncogenes to several adaptor molecules, which are predominantly engaged in the RAS-RAF-MAP kinase pathway (10,11).

Several fusion partners in different types of cancer have been described, and some of them may help in diagnosis, as they are associated with some pediatric and adult rare histological subtypes. For example, the pathognomonic role of ETV6-NTRK3 fusion has been described for the diagnosis of secretory breast carcinoma, mammary analogue secretory carcinoma (MASC) in salivary gland cancers, congenital mesoblastic nephroma (cellular or mixed subtypes), and infantile fibrosarcomas (12,13). In the context of pediatric mesenchymal tumors composed of infiltrating fibroblastic/myofibroblastic tumor cells, other fusion partners besides ETV6-NTRK3 have also been described, such as TMP3-NTRK1, LMNA-NTRK1, and EML4-NTRK3 (13).

Colorectal cancer was the first tumor in which an *NTRK* fusion was detected. Several fusion partners, such as LMNA-NTRK1, TPM3-NTRK1 and ETV6-NTRK3 have been discovered over time, demonstrating the potential involvement of this gene in the development of colorectal cancer and highlighting its important therapeutic implications (14).

The translocation that is widely associated with multiple tumor types is ETV6-NTRK3. This fusion partner of *NTRK3* has been documented in 11 tumor types: glioblastomas, colorectal cancer, MASC (also as salivary gland histologic subtype), ductal carcinomas, fibrosarcomas, congenital mesoblastic nephroma, papillary and radiation-associated thyroid cancer, acute myeloid leukemia (AML), and gastrointestinal stromal tumors (GISTs) (15). LMNA-NTRK1 fusions represent the second most frequently encountered molecular alteration in the landscape of *NTRK* rearrangements. LMNA-NTRK1 has been reported in soft tissue sarcomas (16), lipofibromatosis-like neural tumors (17), sarcomas of young adults (18), congenital infantile fibrosarcoma (19), spitzoid melanomas (20), and spindle cell neoplasms (21). The third most represented *NTRK* fusion partner is TPM3-NTRK1, which has been identified in colorectal cancer (22-24), papillary thyroids carcinomas (25) and glioblastomas (26).

NTRK rearrangements in cancer are relatively rare. Several studies tried to frame their overall prevalence in patients with cancer. One of the largest is a retrospective analysis conducted by Solomon and colleagues in 2020, based on DNA/RNA sequencing of 33,997 cancer patients and reporting *NTRK* fusion in 0.26% of cases (27). Another major study by Rosen *et al.* using a DNA/RNA sequencing approach showed a prevalence of *NTRK* rearrangements of about 0.28% in a population of 26,312 patients (28).

In both studies, the tumor types enriched in *NTRK* fusions were mainly salivary and thyroid gland carcinomas and sarcomas, while in the other tumor types, the prevalence decreased dramatically. Some histological subtypes are strongly associated with *NTRK* fusions, such as secretory carcinomas of the salivary gland and breast or infantile fibrosarcoma (27,28). These data are supported by other studies, such as that of Tognon *et al.*, in which ETV6-NTRK3 expression was found in 92% of secretory breast carcinoma cases (12).

A systematic review and metanalysis conducted by Forsythe *et al.* (29), found the highest *NTRK* gene fusion frequencies in infantile/congenital fibrosarcoma, secretory breast cancer, and congenital mesoblastic nephroma (90.56%, 92.87% and 21.52% of cases, respectively). A lower frequency was reported in NSCLC (0.17%), colorectal adenocarcinoma (0.26%), cutaneous melanoma (0.31%), and non-secretory breast carcinoma (0.60%). For mesothelioma, renal cell carcinoma, prostate cancer and bone sarcoma, the overall frequency of gene fusion in the literature reviewed was about 0%.

Interesting work in the real-world setting was conducted by Westphalen *et al.*, who identified *NTRK* fusion-positive cases through the FoundationCORE® database, finding an overall prevalence of 0.30% among 45 different cancer

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Table 1 List of documented NTRK fusions in lung cancer

Gene	Translocation
NTRK1	MPRIP-NTRK1
	CD74-NTRK1
	SQSTM1-NTRK1
	TPR-NTRK1
	IRF2BP2-NTRK1
	BCL9-NTRK1
	LMNA-NTRK1
	PHF20-NTRK1
	RFWD2-NTRK1
NTRK2	TRIM24-NTRK2
NTRK3	ETV6-NTRK3
	SQSTM1-NTRK3
	EML4-NTRK3

NTRK, neurotrophic tropomyosin receptor kinase.

types, consistent with previously reported data (30). The prevalence of *NTRK* fusions also varied by age: it was 0.28% and 1.34% in patients aged ≥18 and <18 years, respectively, but the highest percentage of 2.28% was observed in pediatric cancer patients younger than 5 years. This study also confirmed the aforementioned higher prevalence of NTRK fusions in salivary gland tumors (2.43%), soft tissue sarcomas (1.27%), and thyroid cancers (1.25%) in adults. Eighty-eight unique fusion partner pairs were identified, of which 58 (66%) had not been previously reported in large, public databases or studies. One of the features of the study, in addition to reporting real-world data, was the analysis of co-alteration patterns. In all the solid tumors included in this analysis, *NTRK* gene fusions were less likely to co-occur with known oncogenes and common factors such as those involved in the MAPK and PI3K signaling pathways, consistent with the hypothesis that tumors caused by molecular alterations in *NTRK* are generally devoid of other canonical oncogenic factors. In the study, co-occurrence was observed with only 14 genes (including *ETV6*, *RNF43*, *IGF1R*, *CDKN2B*, and *CDK4*), while no co-occurrence was reported with *KRAS*, *NRAS*, *BRAF*, *EGFR*, *ALK*, *MET* or *ROS1* (30).

NTRK rearrangements in lung cancer patients

Among *NTRK* fusions, the *NTRK1* gene is the most commonly rearranged in NSCLC. *NTRK1* fusions were first described in NSCLC in 2013 by Vaishnavi *et al.* among a cohort of *EGFR*, *KRAS*, *ALK*, and *ROS1* wild-type lung adenocarcinomas (31). In this study, the authors identified 3 out of 91 patients (3.3%) who had oncogenic fusions of *NTRK1*, specifically MPRIP-NTRK1 and CD74-NTRK1. Their oncogenicity was validated through the expression of a cDNA construct of MPRIP-NTRK1 and CD74-*NTRK1* in three non-cancer cell lines, which induced their independent proliferation leading to the generation of tumors with these genetic features in nude mice (31). Two years later, Farago and colleagues conducted a translational study of a large cohort of 1,378 patients with NSCLC, reporting *NTRK1* gene rearrangements with a frequency of 0.1% (32). The two subjects identified had a TPM3-NTRK1 rearrangement and an SQSTM1-NTRK1 rearrangement. The patient with SQSTM1-NTRK1 fusion transcript expression was enrolled in a phase 1 study with the TKI entrectinib, showing significant clinical and radiological response (32).

Among the *NTRK* rearrangements, TPM3-NTRK1 is the most common one. Other fusion partners of *NTRK1* have been reported for NSCLC, such as TPR, IRF2BP2, BCL9, LMNA, and PHF20, which have been identified in NSCLC as a mechanism of resistance in a subgroup of patients who simultaneously harbored an *EGFR*-activating mutation and were treated with an *EGFR*-TKI (33,34). Rarer histological subtypes of lung cancer also harbor *NTRK1* gene translocations, such as RFWD2-NTRK1 in large neuroendocrine carcinomas of the lung (35). ETV6 and SQSTM1 have been identified as fusion partners for *NTRK3* in NSCLC (33,36). Translocations of *NTRK2* (TRIM24-NTRK2) and *NTRK3* (EML4-NTRK3) have also been described in NSCLC (37,38). Documented *NTRK* fusions in lung cancer have been summarized in *Table 1*.

Given the lower frequency of detection of *NTRK* fusions compared with the other gene rearrangements found in NSCLC (such as *ALK*, *ROS1* and *RET*), it is complex to analyze this type of neoplasm's clinical and pathological features (39).

An initial approach with this aim was conducted by Farago *et al.* in a study involving 47 institutions in the United States, in which 4,872 patients with NSCLC underwent sequencing by next generation sequencing (NGS) (33). The overall frequency of *NTRK* fusions found was 0.23%. The single distribution of *NTRK1*, *NTRK2*, and *NTRK3* fusions was respectively 0.12%, 0.02%, and 0.08%. The histological subtypes of the 11 patients with *NTRK* rearrangement were 9 adenocarcinomas, 1 squamous cell carcinoma, and 1 neuroendocrine carcinoma (33).

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In a retrospective study of 7,395 Chinese NSCLC patients, an overall prevalence of an *NTRK* rearrangement was reported in 0.59% of all cases regardless of histology, 0.61% in adenocarcinomas and 0.5% in squamous cell carcinoma (39). *NTRK* fusion has also been detected in other rare histologic subtypes, such as neuroendocrine carcinoma and sarcomatoid carcinoma (40,41).

In the previously mentioned Westphalen real-world study, an association analysis between *NTRK* rearrangements and other known oncogenic drivers was also performed for NSCLC (30). *NTRK* gene fusions were found to be mutually exclusive with other known NSCLC oncogenic alterations in NSCLC, whereas no mutual exclusivity was found with the presence of a tobacco trinucleotide mutational signature (30).

Methods of detection

The European Society for Medical Oncology (ESMO) has published the results of a 2018 collaborative project led by its Translational Research and Precision Medicine Working Group (TRandPMWG), which proposed a classification system for molecular aberrations, supporting their value as clinical targets, namely the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT) (42). ESCAT has defined six levels of clinical evidence for molecular targets to provide useful recommendations for selecting patients who may benefit from targeted therapies (42).

In 2019, an expert consensus led by the Japan Society of Clinical Oncology (JSCO), the Japanese Society of Medical Oncology (JSMO), ESMO, the American Society of Clinical Oncology (ASCO), and the Taiwan Oncology Society (TOS) outlined the main clinical questions on patients with solid tumors with microsatellite instability or *NTRK* fusions (43). The purpose of the meeting was to produce international consensus recommendations on the use of agnostic tests and treatments in cancer patients. According to this consensus, patients with advanced solid tumors (both unresectable and metastatic) without actionable mutations/fusions/amplifications of driver genes, or who have a high probability of harboring *NTRK* fusions (ETV6-NTRK3 in particular), or who have tumors with characteristics other than those described above, should be tested for *NTRK* fusions. The same working group also defined which tests are recommended for determining *NTRK* fusions in solid tumors. NGS, with gene panels that can detect *NTRK* fusion, is the recommended method of analysis. In situ hybridization (ISH) methods, such as fluorescence in situ hybridization (FISH) and real-time PCR (RT-PCR), are only recommended to detect ETV6-NTRK3 in patients with tumors that have a high probability of harboring *NTRK* fusions (43).

These recommendations are based on the fact that immunohistochemistry (IHC) can examine TRK protein expression but does not directly detects *NTRK* fusions (44). Solomon and colleagues investigated the performance of IHC and next-generation DNA/RNA sequencing to detect *NTRK* fusions indirectly or directly in a very large cohort of 38,095 samples (35). Pan-Trk IHC was shown to have an overall sensitivity of 88%, with lower sensitivity for *NTRK3* fusions, which accounted for the majority of false negatives. DNA-based sequencing had a sensitivity of 81%, with *NTRK2* and *NTRK3* fusions comprising the majority of false negatives. The specificity was greater than 99% for the DNA-based approach, while for IHC it was largely dependent on the type of tumor examined: the specificity of IHC was lower in carcinomas of the breast and salivary glands, while in sarcomas both sensitivity and specificity were poor (27). RT-PCR is only recommended for the detection of ETV6-NTRK3 in tumors with a high prevalence of this molecular alteration (such as secretory breast carcinoma and MASC) because it can only identify known fusion partners and breakpoints. NGS, based on DNA with or without RNA sequencing, is effective for the detection of *NTRK* fusions and has been the primary tool used for genetic analysis in all the above-mentioned studies. It should be recognized that this method may not identify all *NTRK* fusions, especially since the presence of large intronic regions poses DNA-based detection challenges and may lead to the failure to recognize some *NTRK* fusion partners (45). Therefore, NGS panels capable of detecting all *NTRK* rearrangements, regardless of the fusion partner, are recommended for use in clinical practice.

The ESMO Precision Medicine Working Group proposes three levels of recommendations for the use of NGS in patients with metastatic cancers (46). *NTRK* fusion has received grade IC recommendation in non-squamous NSCLC, breast carcinoma, colorectal carcinoma, gastric carcinoma, pancreatic ductal adenocarcinoma, advanced hepatocellular carcinoma, and cholangiocarcinoma. This recommendation is based on the fact that clinical basket trials have demonstrated a benefit of overlapping magnitude and distribution for the drug-target pair in different tumor types, and therefore information on the molecular status of *NTRK* could improve treatment options for these patients.

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The group recommends the use of multigene sequencing to detect *NTRK* fusions only in cancers for which this technology is otherwise recommended. Cheaper alternative methods should be preferred for screening *NTRK* fusions in countries where TRK inhibitors are available (46).

The health care, pharmaceutical, and diagnostic industries are embarking on a path in which the development of new diagnostic tests and related complementary drugs travel together. According to the FDA definition, a companion diagnostic is a medical device, often an in vitro diagnostic (IVD), that provides essential information for the safe and effective use of a corresponding drug or biological product (47). In this context, the FDA approved FoundationOne CDx test to identify *NTRK1*, *NTRK2* and *NTRK3* fusions in DNA isolated from tumor tissue samples of patients with solid tumors eligible for treatment with larotrectinib and entrectinib. Companion diagnostics can identify patients who are more likely to benefit from a particular therapeutic product, patients who may be at greater risk of serious treatment-related side effects, or monitor response in terms of safety or efficacy. Companion diagnostics are regulated by the FDA and the EMA. In May 2017, Regulation 2017/746 on in vitro diagnostic medical devices (IVDR) came into force in Europe, under which these medical devices will be classified as class C devices and will require specific conformity assessments. To date, companion diagnostics in Europe are not yet associated with drug approval and prescription, so *NTRK* fusions can be detected by one of the methods mentioned by ESMO or national guidelines. Of all, the preferred one is NGS, especially for NSCLC.

Targeting NTRK fusions: TRK inhibitors in the treatment of NTRK-positive cancers

First-generation *NTRK* inhibitors

Currently, for patients with tumors harboring *NTRK1/2/3* rearrangements, two first-generation targeted agents are commercially available: larotrectinib and entrectinib.

NTRK inhibitors are TRK inhibitors, which prevent ligand-TRK interaction and subsequent TRK activation, thus blocking cellular oncogenic activity. First-generation TRK inhibitors have been studied in clinical trials since 2015. Due to the rarity of *NTRK* fusions, these trials have mainly been basket-type studies enrolling patients with different tumor types and histology.

Larotrectinib is the first selective TrkA/B/C inhibitor to be approved for the treatment of TRK fusion-positive solid tumors in children and adults. In 2018, Drilon and colleagues published the results of three phase 1/2 studies, LOXO-TRK-14001 (NCT02122913), SCOUT (NCT02637687) and NAVIGATE (NCT02576431), that evaluated efficacy and safety of larotrectinib in adults and children who had tumors with *NTRK* fusions (48). The three studies enrolled a total of 55 patients, aged 4 months to 76 years, with 17 TRK fusion-positive tumor types. The overall response rate (ORR), the primary objective of the study, was 75% [95% confidence interval (CI): 61% to 85%] according to the independent review and 80% (95% CI: 67% to 90%) according to the investigator's assessment. At a median follow-up of 9.4 months, 86% of responding patients were continuing treatment or had undergone curative surgery. The most common adverse events, all grade 1 and 2, included anemia (11%), decreased neutrophil count (7%), increased transaminases (7%) and weight gain (7%). Grade 3 adverse events occurred in less than 5% of patients, while there were no treatment-related grade 4 or 5 events, according to the investigators (48). These data led to the FDA's accelerated approval of larotrectinib for adult and pediatric patients with *NTRK* gene fusion-positive solid tumors in November 2018. The EMA approved larotrectinib in July 2019 as the first agnostic TKI in Europe. Larotrectinib is administered orally at a dose of 100 mg twice daily in adults. In pediatric patients, the dose is calculated according to body surface area, and the recommended dose is 100 mg/m^2 twice daily. Larotrectinib is administered until disease progression or the appearance of unacceptable toxicity.

Entrectinib is a tropomyosin receptor tyrosine kinase TrkA/B/C, proto-oncogene tyrosine-protein kinase *ROS1*, and anaplastic lymphoma kinase (*ALK*) inhibitor. Entrectinib was studied in four phase 1/2 clinical trials, three conducted in adult patients with *NTRK* fusion-positive tumors (STARTRK-1, STARTRK-2, ALKA-372-001) and one in children and young adults with solid or primary central nervous system (CNS) tumors that had *NTRK* fusion or *ROS1* and *ALK* aberrations (STARTRK-NG) (49). Doebele and colleagues conducted an integrated efficacy and safety analysis of the first three studies (50) (*Table 2*). Fifty-four adult patients with 10 different tumor types and 19 histologies were evaluated. At a median follow-up of 12.9 months, 57% (95% CI: 43.2–70.8%) of patients had an objective response, including 7% complete responses (CRs), with a mDOR of 10 months (95% CI: 7.1 to not estimable). The authors also reported data on the intracranial (IC) activity of entrectinib: of the

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Table 2 Summary of key clinical trials of first generation *NTRK* inhibitors

Study name	Clinical trial	Phase	Drug	Number of patients	ORR (95% CI)	Safety	Status (at 30/07/2023)
LOXO-TRK-14001	NCT02122913	1	Larotrectinib	55	75% (61–85%)	G3: <5%; G4/5: 0%	Completed
SCOUT	NCT02637687	1/2					Active, non recruiting
NAVIGATE	NCT02576431	2					Active, non recruiting
STARTRK-1	NCT02097810	1	Entrectinib	54	57% (43.2–70.8%)	G3: 61%; G4: 9%; G5: 0%	Completed
STARTRK-2	NCT02568267	2					Active, not recruiting
ALKA-372-001	NCT02097810	1					Completed

NTRK, neurotrophic tropomyosin receptor kinase; ORR, overall response rate; CI, confidence interval; G, grade.

11 patients with encephalic metastases at baseline, 55% had an IC response. More than half had received previous radiotherapy. Among the treatment-related adverse events, most were grade 1–2 and reversible (dysgeusia, constipation, diarrhoea, fatigue, oedema). The most common grade 3–4 adverse events were weight gain and anemia. Nervous system disorders, including dizziness and cognitive impairment, were the most common serious treatment-related adverse events (50). Based on these data, in August 2019 the FDA granted accelerated approval of entrectinib for adult and pediatric patients aged 12 years and older with solid tumors harboring *NRTK* fusions. In 2020, the drug also received EMA approval. Entrectinib is administered in adults at the dose of 600 mg orally once daily. The recommended dose in pediatric patients 12 years of age and older is 300 mg/m^2 of body surface area once a day.

Iannantuono *et al.* evaluated the benefit of TRK inhibitors (larotrectinib and entrectinib) in a virtual cohort of patients with *NTRK* gene fusion-positive solid tumors derived from a systematic review of the literature through case reports and case series (51). Thirty-eight publications, 32 case reports and 6 case series, published between 2018 and 2022, were included. The virtual cohort consisted of 43 patients, 25 adults and 18 pediatric, with a mean age of 37 years (range, <1–81 years). In the overall population, the most frequent types of cancer were soft tissue sarcomas (30.2%), tumors of the CNS (27.9%), thyroid (14%), salivary glands (9.3%) and lung (4.8%). Other less represented cancer types were cervical, breast, colon, ovarian, pancreatic and thymoma. Most of the patients (79.1%) were on TRK inhibitor therapy for advanced disease, and 90.7% of them had received previous treatment. *NTRK* gene rearrangements detected involved *NTRK1* in 25.6%, *NTRK2* in 16.3% and *NTRK3* in 51.2% of cases. In 7% of patients, the specific *NTRK* gene involved was not reported. Larotrectinib and entrectinib were administered in 81.4% and 16.3% of patients, one patient (2.3%) received both drugs. The best radiological response was a partial response (PR) in 74.5% of patients, while CR was achieved in 20.9% of cases. At the time the article was published, about 72% of patients were alive with the disease (51). The publication of case reports plays an essential role in increasing medical knowledge about rare conditions, such as neoplasms with *NTRK* gene alterations. The creation of a virtual cohort of patients based on case reports and case series provides a single source of easily accessible data and the ability to make indirect comparisons with populations enrolled in clinical trials. The data obtained from this virtual cohort are in line with those available in the literature and confirm that TRK inhibitors represent an effective therapeutic strategy for this subgroup of patients.

Efficacy of TRK inhibition in NSCLC patients

Efficacy data of larotrectinib from the 20 lung cancer patients enrolled in the LOXO-TRK-14001 and NAVIGATE trials were recently released (52). The baseline characteristics of patients with lung cancer were as follows: median age 48.5 years (range, 25.0–76.0 years), ECOG Performance Status 0 or 1 in 90% of cases, histology of adenocarcinoma in 19 patients and neuroendocrine carcinoma in 1 patient. Half of them had metastases to the CNS at baseline, including two cases previously treated with radiotherapy. *NTRK* fusions were identified by RNA-based sequencing in 35% of patients and by targeted DNA-based NGS in 65% of patients. Sixteen of the 20 patients had *NTRK1* fusions [fusion partners: TPM3 (n=6), EPS15 (n=2), IRF2BP2 (n=2), NOS1AP (n=1), SQSTM1 (n=1), TPR (n=1), CD74 (n=1), CLIP1 (n=1) and PRDX1 (n=1)] and 4 out of 20 of *NTRK3* [fusion partners: SQSTM1 (n=2) and ETV6 (n=2)]. The enrolled patients were heavily pretreated, with a median of

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Table 3 Summary of outcomes of NSCLC patients treated with TRK inhibitors

Study (ref.)	Drug	NSCLC patients	ORR (95% CI)	mDOR (95% CI), months	Patients with CNS mts	IC ORR	mOS (95% CI), months	mPFS (95% CI), months
LOXO-TRK-14001, NAVIGATE (52)	Larotrectinib	20	73% (45–92%)	33.9 (5.6–33.9)	8	NA	NA	35.4 (5.3–35.4)
Iannantuono *et al.* (51)	Larotrectinib	2	NA; PRs	NA	NA	NA	NA	NA
STARTRK-1 (50)	Entrectinib	13	69% (38.6–90.9%)	NE (5.6–NE)	8	62.5%	14.9 (5.9–NE)	14.9 (4.7–NE)
STARTRK-2 (53)								
ALKA-372-001 (54)								

NSCLC, non-small cell lung cancer; TRK, tropomyosin receptor kinase; ref, reference; ORR, overall response rate; CI, confidence interval; mDOR, median duration of response; CNS, central nervous system; mts, metastases; IC, intracranial; mOS, median overall survival; mPFS; median progression-free survival; NA, not available; PRs, partial responses; NE, not estimated.

3 previous lines of systemic therapy (range, 0–6). Six patients had previously received immune checkpoint inhibitors. The investigator-assessed ORR among the 15 evaluable patients was 73% (95% CI: 45–92%); 1 patient had a CR, 10 patients had a PR, 3 had stable disease (SD), and 1 had progressive disease (PD) as the best response. At the time of data cut-off, treatment was ongoing in 11 patients (55%). The median time to response was 1.8 months (range, 1.6–1.9 months), corresponding to the first restaging examination of the study. The median duration of response (mDOR) was 33.9 months (95% CI: 5.6–33.9) at a median follow-up of 17.4 months. Median progression-free survival (mPFS) was 35.4 months (95% CI: 5.3–35.4); PFS rates at 12 and 24 months were 65% and 55%, respectively. All 8 evaluable patients with CNS metastases at baseline had reductions in target systemic lesions ranging from 18% to 88%. The investigator-assessed ORR was 63% (95% CI: 25–91%); 5 patients had PRs, 2 had SD, and 1 had PD. Adverse events were mostly grade 1 or 2, and no new or unexpected safety signals emerged (52).

In the previously mentioned virtual cohort of patients with *NTRK* fusion-positive solid tumors treated with TRK inhibitors by Iannantuono *et al.* (51), 2 patients (4.8%) had advanced NSCLC. The data derives from two clinical cases present in the literature. Both patients had adenocarcinomatous histology, had *NTRK1* fusions (TPM3-NTRK1 and NCOR2-NTRK1 as fusion partners), and were treated with larotrectinib, achieving RP in both cases with a DOR of 4 and 15 months, respectively (51).

Regarding the efficacy of entrectinib in patients with *NTRK*+ lung cancer, data came from the integrated analysis of STARTRK-1, STARTRK-2 and ALKA-372-001 trials by Doebele (50) and from the update analysis by Drilon and colleagues (53). Thirteen patients had NSCLC with *NTRK* fusions (*NTRK1*: 8, *NTRK2*: 1, *NTRK3*: 4). The median age was 60 years (range, 46–77), 69% of patients had adenocarcinoma histology, 9 patients had CNS metastases at baseline, 5 patients had received more than two prior systemic therapies. Entrectinib was active in NSCLC patients with and without CNS metastases, with an ORR of 69% (95% CI: 38.6–90.9%) in the total subpopulation of lung cancer patients and 67% (95% CI: 29.9–92.5%) in patients with IC disease. Median overall survival (mOS) in NSCLC patients was 14.9 months (95% CI: 5.9–NE), mPFS 14.9 months (95% CI: 4.7–NE), while mDOR was not estimated. Median OS was 8.9 months (95% CI: 5.6–NE) and mPFS was 6.5 months (95% CI: 4.5–NE) in NSCLC patients with IC disease at baseline, while survival data were not estimated in patients without CNS metastases (53). The IC ORR in the subpopulation of 8 patients with NSCLC who had measurable or unmeasurable CNS metastases at baseline was also 62.5%, with three CRs and two PRs; it was 60% in the subpopulation of five patients with CNS measurable disease (54). Entrectinib induced clinically significant responses in patients with locally advanced or metastatic *NTRK*+ lung cancer, regardless of the presence or absence of CNS metastases at baseline.

The main results illustrated in this paragraph are summarized in *Table 3*.

Resistance to TRK inhibition: on-target and off-target mechanisms

Despite the high clinical activity of larotrectinib and entrectinib, cases of acquired resistance to TRK inhibition, mediated by on-target and off-target mechanisms, have

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been reported (55).

On-target resistance occurs through mutations in the *NTRK* kinase domain of the oncogenic fusion gene, involving amino acid substitutions in three major regions: the solvent front (e.g., TRKAG595R, TRKBG639R, TRKCG623R), the xDFG motif (e.g., TRKAG667C, TRKBG709C, TRKCG696A), and the gatekeeper residue (e.g., TRKAF589L, TRKBF633L, TRKCF617L) (56). These mutations can substantially alter the conformation of the TRK kinase domain by causing steric hindrances or by changing the binding affinity to ATP (57). These alterations are paralogous to resistance mutations found in other oncogene-dependent tumors that progress to tyrosine kinase inhibitors (TKI) therapy. For example, TRK solvation front mutations are paralogous to those in ALKG1202R and ROS1G2032R, TRK xDFG substitutions are paralogous to those in ALKG1269A, TRK gatekeeper mutations are paralogous to those in ALKL1196M and ROS1L2026M (58,59). The first case of acquired resistance to TRK inhibition was reported in a patient with rearranged LMNA-NTRK1 colorectal cancer after 4 months of treatment with entrectinib (60). Sequencing of cfDNA revealed two kinase domain mutations that led to the two substitutions G595R in the solvent front region and G667C at the "x" position of the xDFG domain (60).

Off-target resistance mechanisms are characterized by the activation of non-TRK oncoproteins that mediate parallel cell signaling pathways in order to evade blockade by on-target TKIs. Cocco *et al.* reported the off-target resistance mechanisms identified in a series of gastrointestinal cancer patients treated with TRK inhibitors. Resistance in these cases was mediated by genomic alterations that converge in the activation of the MAPK pathway (61). *MET* amplification, *BRAFV600E* mutation, and *KRAS* mutations were identified in tissue and circulating cell-free DNA (cfDNA) samples obtained prospectively from study subjects. Once mechanisms of resistance were identified, patients were treated with therapy targeting the MAPK pathway (dabrafenib and trametinib for the *BRAFV600E* mutation and crizotinib for *MET* amplification), given alone or in combination, achieving a restoration of disease control. Cell line-derived xenografts from these patients were more sensitive to combination therapy than to either single agent and less sensitive to the use of new generation TRK inhibitors given alone (61). Another off-target resistance mechanism identified in *in vitro* models is the activation of the insulin like growth factor 1 receptor (IGF-1R) (62).

Second generation TRK inhibitors

Repotrectinib (TPX-0005) and selitrectinib (LOXO-195, BAY2731954) are the leading second-generation TRK inhibitors in clinical development that can inhibit most of the on-target resistance mutations of *NTRK*. The new generation inhibitors have lower molecular weight and a compact macrocyclic structure than those of the first generation. This type of structure circumvents the steric hindrance that prevents first-generation inhibitors from binding to the ATP-binding site at the solvent front, gatekeeper and xDFG mutations (63).

Repotrectinib is a second-generation *ROS1* and TRK inhibitor. It is a smaller compound than the other *ROS1*, *TRKA-C* and *ALK* inhibitors, designed to accommodate, without any steric hindrance, the bulky positively charged arginine side chain in the solvent front (TRKA G595R, TRKB G639R and TRKC G623R) (64). The small size of the drug also favors its penetration into the CNS (63). Clinical activity of repotrectinib is being evaluated in the phase 1/2 TRIDENT-1 study (NCT03093116), which enrolled patients with advanced solid tumors harboring *ALK*, *ROS1*, or *NTRK1/2/3* rearrangements. Besse and colleagues reported an update of the TRIDENT-1 study regarding patients with *NTRK* fusions enrolled in expansion cohorts 5 (TKI naive, 8 patients) and 6 (pretreated, 19 patients) (65). The confirmed ORR (cORR) in TKI naive and pretreated patients were 63% (95% CI: 24–91%) and 47% (95% CI: 24–71%), respectively. In 10 patients in cohort 6 who had a solvent front mutation, cORR was 60% (95% CI: 26–88%). At the updated safety analysis conducted on the entire study population for phases 1 and 2, repotrectinib was generally well tolerated. The most frequent treatment-related adverse events observed in ≥20% of patients were dizziness (62%), dysgeusia (43%), constipation (33%), dyspnea (30%), paresthesia (28%), fatigue (26%) and anemia (26%). Twenty-four percent of patients had a dose reduction and 10% discontinued the drug due to toxicity (65). With the first interim data from the TRIDENT-1 trial, the FDA has granted breakthrough therapy designation to repotrectinib for the treatment of patients with solid tumors carrying an *NTRK* gene fusion that have progressed after being treated with 1 or 2 previous TRK TKIs plus or minus chemotherapy. The drug had previously received designation as a breakthrough therapy for *ROS1*-positive metastatic NSCLC not undergoing *ROS1*-TKIs.

Selitrectinib is an orally bioavailable, selective TRK

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inhibitor in development. To date, there are no data available about its clinical activity, but some case reports showed promising efficacy in patients progressed to entrectinib or larotrectinib (66,67). Selitrectinib is being evaluated in phase 1 study NCT03215511 and in expanded access NCT03206931.

Taletrectinib (AB-106/DS-6051b) is a novel brain-penetrating *ROS1* and *NTRK* TKI. Results of the first human phase 1 study of taletrectinib were reported by Papadopolous and colleagues in 2020 (68). Forty-six patients with neuroendocrine tumors, tumor-induced pain, or tumors with *ROS1/NTRK* rearrangements were enrolled. Taletrectinib was shown to have a manageable safety profile and long-term tolerability at the maximum tolerated dose of 800 mg daily. The most common treatment-related toxicities were gastrointestinal, such as nausea (47.8%), diarrhea (43.5%) and vomiting (32.6%). Reductions in pain scores were also observed. Preliminary efficacy was reported in patients with crizotinib-refractory *ROS1*+ NSCLC (68).

Conclusions

The TRK family has become the subject of clinical interest because the *NTRK1/2/3* genes encoding them have been identified as oncogenes in a wide variety of pediatric and adult malignancies, including NSCLC. In recent years, advances in molecular diagnostics have led to a sea change in the treatment of cancer patients, moving from a "one-size-fits-all" therapeutic model to a "personalized" approach through the development of new agents targeting specific genomic aberrations. *NTRK* fusions represent an infrequent molecular alteration, but can benefit from targeted therapy with good response that has been shown to be uniform across tumor types.

Testing for *NTRK* fusions should be part of standard molecular testing for newly diagnosed NSCLC patients. The first-generation TRK inhibitors, larotrectinib and entrectinib, have been studied in phase 1/2 clinical trials in patients with both adult and pediatric solid tumors, demonstrating good tolerability and a high response rate regardless of tumor type treated, fusion type, and age. The approval of larotrectinib and entrectinib for patients with *NTRK* gene fusion tumors represented a milestone in the era of "agnostic" drugs. Since *NTRK* fusions are present in many tumor types, the test could also be performed in other histologies and malignancies that require DNA sequencing. A recent analysis of the cost-effectiveness of targeted treatment in patients with *NTRK*-positive tumors showed that testing for *NTRK* fusions and treating positive patients with entrectinib resulted in increased per-patient quality-adjusted life years and costs compared with not testing for *NTRK* and treating patients with the standard of care, consistent with the limitations of the analysis data (69). The number of tests needed to identify patients eligible for entrectinib is certainly high, compared with the low prevalence of *NTRK* fusions. The authors conclude that if genetic testing of cancer patients becomes standard practice, treatment with entrectinib could be cost-effective (69).

Despite the high activity of first-generation agents, acquired resistance to TRK inhibitors is a clinical issue. On-target resistance can be overcome with next-generation TRK inhibitors, which are currently in clinical trials. There are still few data on the optimal sequence of treatment with TRK inhibitors. It will be interesting to see whether next-generation *NTRK* inhibitors should be administered only after failure of the previous line or whether their use will be advanced to the first line of treatment.

In conclusion, *NTRK* fusions represent a new and interesting therapeutic target, and the TKI entrectinib and larotrectinib, as agnostic drugs, are an important achievement in precision medicine and an effective treatment option for a small, but increasingly less negligible, subgroup of patients.

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Footnote

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