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NTRK gene fusion testing and management in lung cancer

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ABSTRACT

Neurotrophic tyrosine receptor kinase (*NTRK*) gene fusions are recurrent oncogenic drivers found in a variety of solid tumours, including lung cancer. Several tropomyosin receptor kinase (TRK) inhibitors have been developed to treat tumours with *NTRK* gene fusions. Larotrectinib and entrectinib are first-generation TRK inhibitors that have demonstrated efficacy in patients with TRK fusion lung cancers. Genomic testing is recommended for all patients with metastatic non-small cell lung cancer for optimal drug therapy selection. Multiple testing methods can be employed to identify *NTRK* gene fusions in the clinic and each has its own advantages and limitations. Among these assays, RNA-based next-generation sequencing (NGS) can be considered a gold standard for detecting *NTRK* gene fusions; however, several alternatives with minimally acceptable sensitivity and specificity are also available in areas where widespread access to NGS is unfeasible. This review highlights the importance of testing for *NTRK* gene fusions in lung cancer, ideally using the gold-standard method of RNA-based NGS, the various assays that are available, and treatment algorithms for patients.

Introduction

In non-small cell lung cancer (NSCLC), oncogene dysregulation due to activating mutations, fusions or amplifications is a frequent event. These recurring oncogenic alterations enable cancer cell survival and growth [1,2]. Lung cancers harbouring oncogenic drivers tend to rely on aberrant signalling for survival and growth, a concept known as 'oncogene addiction' [2,3]. This dependency on oncogene signalling, however, generates a unique vulnerability that can be exploited with the use of selective targeted agents such as tyrosine kinase inhibitors (TKIs) [2,4]. TKIs reduce the replicative fitness of cancer cells and cause apoptosis, with the ultimate clinical goal of controlling disease morbidity and improving patient outcomes [2,4].

This tumour biology-informed treatment strategy has been extensively proven to be viable for treating patients with oncogene-addicted NSCLCs, leading to the approval of multiple oncogene-directed therapies for patients in the last decade [4,5]. This same wave of approvals concurrently played a role in promoting the routine use of molecular testing in patients with lung cancer [6]. Diagnostic advancements fuelled by the need to reliably and cost-effectively match patients to targeted therapy has resulted in improved assay sensitivity and comprehensiveness.

As of 2023, targeted therapies are approved by one or more regulatory agencies for patients with metastatic NSCLC harbouring select sensitising alterations in epidermal growth factor receptor (*EGFR*), human epidermal growth factor receptor 2 (*HER2*, also known

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as *ERBB2*), B-type Raf proto-oncogene (*BRAF*), mesenchymal epithelial transition (*MET*), anaplastic lymphoma kinase (*ALK*), rearranged during transfection (*RET*), c-ros oncogene 1 (*ROS1*) and neurotrophic tyrosine receptor kinase (*NTRK*)*1/2/3* [3,7]. Targeted therapy for *NTRK* gene fusions achieves impressive activity that is either comparable to or exceeds that of targeted therapy for other oncogenic drivers, underlying the importance of understanding the biology of these fusions, finding them in patient samples and developing an approach to therapy selection and adverse-event (AE) management.

NTRK gene fusion biology

Normal TRK physiology

The *NTRK1*, *NTRK2* and *NTRK3* genes encode the tropomyosin receptor kinase (TRK) receptors A, B and C, respectively [8]. Although TRKA/B/C proteins play key roles in embryonic development, physiologic expression is restricted to a few cell types like smooth muscle, neuronal components and testes in adults [9–12]. Under physiologic circumstances, neurotrophin ligand-binding and TRK activation initiate homodimerisation of the receptor, which subsequently leads to the transactivation of TRK intracellular domains. This is followed by the engagement of cytoplasmic adaptor proteins; these adaptors instigate downstream signalling through the activation of the mitogen-activated protein kinase (MAPK), phosphoinositide-3-kinase and/or protein kinase C pathways [13].

Primary oncogenesis with TRK fusion proteins

NTRK gene fusions are rare but recurrent oncogenic drivers found in up to 1% of all solid tumours [8]. In NSCLCs, the frequency of *NTRK* gene fusions is estimated to be 0.1–0.2% [14–17]. *NTRK* gene fusions generally arise when the 3′ segment of *NTRK1/2/3*, which encodes the kinase domain, is combined with a different gene in the 5′ position through intra- or inter-chromosomal rearrangement. The resultant fusion protein comes under the regulation of the promoter of the partner gene. Consequently, the transcriptional programme active in the fusion-positive cell leads to anomalous signalling mediated by the aberrantly expressed TRK fusion proteins [8,18]. Consistent with their role in strongly promoting oncogenesis, *NTRK* gene fusions are usually mutually exclusive with other canonical oncogenic alterations [17,19,20].

Most patients with lung cancers harbouring *NTRK* gene fusions share similar clinical features with *ALK*, *RET* or *ROS1* fusion-positive lung cancers, specifically a younger median age compared with non-oncogene-addicted lung cancers and minimal or no prior history of cigarette smoking. However, *NTRK* gene fusions are identified in patients across a variety of ages and prior smoking histories [1,14]. Central nervous system (CNS) metastases have been identified in many patients with TRK fusion lung cancers, consistent with that seen in other lung cancers driven by oncogenes [21–24].

NTRK point mutations, splice variants and copy number gain/amplification have also been observed in some tumour types. However, these alterations have not been strongly associated with targeted therapy benefit thus far, and their actionability is considered limited or absent [25,26].

TRK fusion acquisition in TKI resistance

Aside from their well-characterised role as primary drivers of oncogenesis, *NTRK* gene fusions can also arise as acquired resistance mechanisms to targeted therapy directed against other oncogenes. In this setting, the evolutionary pressure applied by the inhibition of the founder oncogene favours the selection of a new cancer cell population harbouring a gene fusion able to withstand the precedent non-TRK-fusion-directed treatment [27–29].

NTRK gene fusions can be causative or putative resistance mechanisms to EGFR TKI treatment in patients with *EGFR*-mutant NSCLC [27–30]. In a series of 21,155 lung cancers in China, there were six patients with existing *EGFR* mutations previously treated with EGFR TKIs who had co-existing *NTRK1* gene fusions [28]. Although it is unclear if an analysis of paired pre-treatment and post-treatment samples was performed in this study, the authors concluded that these *NTRK* gene fusions were presumptively the reason for acquired resistance to EGFR inhibitor treatment. These observations of acquired *NTRK* gene fusions as a resistance mechanism to the evolutionary pressure applied by a TKI are in line with a similar phenomenon observed with other acquired fusions post-EGFR TKI progression, such as *RET*, *ALK* or *FGFR3* fusions [30,31]. Although to date no case reports have reported the occurrence of *NTRK* gene fusions as an acquired resistance mechanism to the inhibition of other oncogenes such as *RET*, *ROS1* or *ALK*, this phenomenon might also be possible.

Overall, although acquired *NTRK* gene fusions are a rare occurrence, precision-medicine case reports highlight the feasibility of the simultaneous addition of a TRK inhibitor to the prior treatment to target the acquired *NTRK* gene fusion [27].

Identifying *NTRK* gene fusions

Several different tests can detect *NTRK* gene fusions. These tests include immunohistochemistry (IHC), fluorescence *in situ* hybridisation (FISH), reverse transcription-polymerase chain reaction (RT-PCR) and next-generation sequencing (NGS) [32,33]. *NTRK* gene fusion identification using liquid biopsies, such as circulating tumour DNA (ctDNA) assays, is also feasible [34]. Each detection method has intrinsic advantages and limitations [32,35]. As such, testing strategies used in the clinic need to balance reliability and scalability with analytical specimen characteristics and local test availability.

Comprehensive testing

NGS of tumour tissue is considered the gold standard, as it is the most comprehensive and inclusive method of identifying *NTRK* gene fusions while also allowing the detection of concurrent non-*NTRK* gene alterations (Table 1). NGS assays can be based on the analysis of either DNA or RNA, with some variability in gene coverage based on the technology platform used [32,35–37]. DNA-based NGS assays need to tile introns for accurate fusion detection; however, some intronic regions (e.g., *NTRK2*) are too large to be captured by DNA-based approaches. Consequently, some *NTRK* gene fusions can be missed [32]. RNA-based NGS avoids these limitations by enriching for specific expressed transcripts without the need for large introns [32]. These assays may also include information on transcriptional activity and frame retention of the fusion gene.

While RNA-based NGS has advantages compared to DNA-based NGS, intrinsic limitations of these detection methods should also be considered, as amplicon-based and hybrid capture-based approaches both have specific requirements. Fusion detection with amplicon-based NGS is most reliable for gene partners that are known and included in the primer pool, as only these will be amplified and sequenced. While some strategies exist to detect the presence of a fusion event for unknown partners, such as the observation of a 3′/5′ imbalance in reads, they do not allow the clear identification of the partner gene and may require further confirmatory analysis [38]. On the other hand, hybrid capture-based approaches allow detection of gene fusions even if they are complex and the primer-binding sites for amplicon-based NGS have been lost; however, they generally require higher nucleic acid input quantities [39].

ctDNA NGS is a minimally invasive technique that can also be used to identify *NTRK* gene fusions (Table 1). Sensitivity can be a challenge with ctDNA analysis as detection of genetic alterations requires adequate tumour cell shedding for detection in the circulation [40], and is also influenced by therapy response and disease burden. Furthermore, the *NTRK* gene fusion probe regions require high coverage due to the large

Table 1
Comparison of the various methods used to test for *NTRK* gene fusions [32,33,44].

	IHC	FISH	RT-PCR	NGS
Advantages	• Widely used • Cost effective • ~1–2 days' turnaround time	• Widely available • Approximately 3–5 days' turnaround time • Can detect the presence of a fusion event involving a target gene without prior knowledge of the fusion partner	• Highly specific • Sensitive • Approximately 1-week turnaround time • Multiplexing capabilities	• Most comprehensive and inclusive • Can be based on either the analysis of DNA or RNA • ctDNA NGS can serve as a surrogate method when a tissue specimen is not available
Disadvantages	• Pan-TRK antibody does not discriminate between expression of the wild-type and fusion protein • May be used as initial screening, but requires confirmation with secondary method	• Can be labour- and cost-intensive as individual analyses must be performed for each of the three *NTRK* genes	• Requires prior knowledge of the fusion partners	• Costly • RNA NGS requires optimal tissue fixation • Technically complex • DNA NGS risks false negatives • Approximately 1–3 weeks' turnaround time • Sensitivity varies among partner genes • ctDNA NGS requires adequate tumour cell shedding for detection in the circulation

ctDNA: circulating tumour DNA; FISH: fluorescence *in situ* hybridisation; IHC: immunohistochemistry; NGS: next-generation sequencing; *NTRK*: neurotrophic tyrosine receptor kinase; RT-PCR: reverse transcription-polymerase chain reaction; TRK: tropomyosin receptor kinase.

number of possible partner genes. To ensure a high sequencing depth, ctDNA panels normally target limited probe regions without complete coverage across *NTRK1/2/3*; this may result in an increase in false negatives [41].

Given the aforementioned limitations of ctDNA-based NGS in detecting *NTRK* gene fusions and the somewhat high chance of false-negative results, the 2022 European Society for Medical Oncology (ESMO) recommendations on the use of ctDNA assays for patients with cancer state that a tissue-based assay should be repeated when possible if ctDNA is negative [42].

Finally, serial ctDNA testing can monitor tumour response and growth in patients treated with TRK inhibitors [40]. In an analysis assessing concordance between the ctDNA-based NGS Foundation One® Liquid CDx (F1L CDx) and tumour DNA- or RNA-based NGS testing used to identify patients with tumours that harbour *NTRK* gene fusions in a phase 2 basket entrectinib trial, the positive percentage agreements between F1L CDx and clinical trial assays was 47.4% for *NTRK* gene fusions among 85 evaluable pre-treatment clinical samples, with F1L CDx demonstrating a positive predictive value of 100% for *NTRK* gene fusion-positive samples. F1L CDx testing also identified acquired resistance mutations across a range of tumour types with *NTRK* gene fusions. These data suggest that F1L CDx is a clinically valid non-invasive complement to tissue-based testing in identifying patients with cancers harbouring actionable oncogenic biomarkers and those with acquired resistance mutations, and may be a testing option for patients who do not have adequate or available tissue samples for NGS testing [43].

Single/oligo gene testing

As NGS may be limited in availability in certain areas due to cost and technical complexity, alternative testing methods can be used. FISH can detect the presence of a fusion event involving a target gene without prior knowledge of the fusion partner and is available in most clinical laboratories [32,33]. On the other hand, FISH is labour- and cost-intensive, as individual analyses must be performed for each of the three *NTRK* genes [32,33].

RT-PCR is a highly specific, rapid and sensitive method with a quick turnaround time (~1 week) and multiplexing capabilities. This method, however, is not fusion-partner-agnostic as it requires prior knowledge of fusion partners [32,33,40,44], of which many exist (Fig. 1) and several may yet be unknown.

Protein expression testing

IHC is a widely used technique to screen for *NTRK* gene fusions and has a fast turnaround time (~1–2 days) [32,33,45,46]. If high-quality IHC is implemented, the use of a pan-TRK antibody has high sensitivity [46,47] for detecting TRK expression [9]. The pan-TRK antibody does not discriminate between expression of the wild-type and fusion proteins [32,48]; therefore, confirmation with a secondary method, such as NGS, is required (Table 1) [32,33]. Conversely, IHC can be used as a confirmation assay for protein expression in cases detected by NGS or FISH, particularly when equivocal results are obtained (e.g., if a fusion of unclear significance is found) [9,46,47].

Testing recommendations

Testing practices for *NTRK* gene fusions differ by country due to varying accessibility and availability of tests and treatment options [49]. Global recommendations for *NTRK* gene fusion testing are shown in Table 2. The choice of testing method should account for factors such as tumour type and prevalence of *NTRK* gene fusions in that tumour type [9,50].

The National Health Commission of the People's Republic of China guidelines suggest testing in advanced NSCLC whenever feasible [51]. Canadian guidelines similarly advocate for routine testing in advanced NSCLC cases [52]. The ESMO guidelines mandate subtyping of all NSCLCs for therapeutic decision-making, and recommend testing for *EGFR*, *ALK*, *ROS1*, *NTRK*, *RET*, *BRAF*, *ERBB2*, *KRAS* and programmed death-ligand 1 (PD-L1) status in all patients with advanced NSCLC [53,54] and suggest molecular subtyping should be performed for patients with early-stage NSCLC when feasible [42]. Most guidelines recommend comprehensive molecular diagnostics for patients with advanced-stage disease only, however there is an ever-growing rationale for extending testing to all patients with NSCLC. Presently, the only established targeted agent in early-stage NSCLC is osimertinib for *EGFR* mutation-positive patients [55], however, ongoing clinical studies, like NAUTIKA1 [56], are investigating the role of TRK inhibition in this setting. While testing for early-stage patients can undoubtedly add options in terms of investigational treatments, achieving a scenario where blanket comprehensive genetic testing is performed in the early-stage setting has several challenges, since *NTRK* testing coverage is sometimes suboptimal, even for patients with advanced disease.

Given that TRK inhibitors are approved in a tumour-agnostic fashion in multiple countries, several international oncology societies

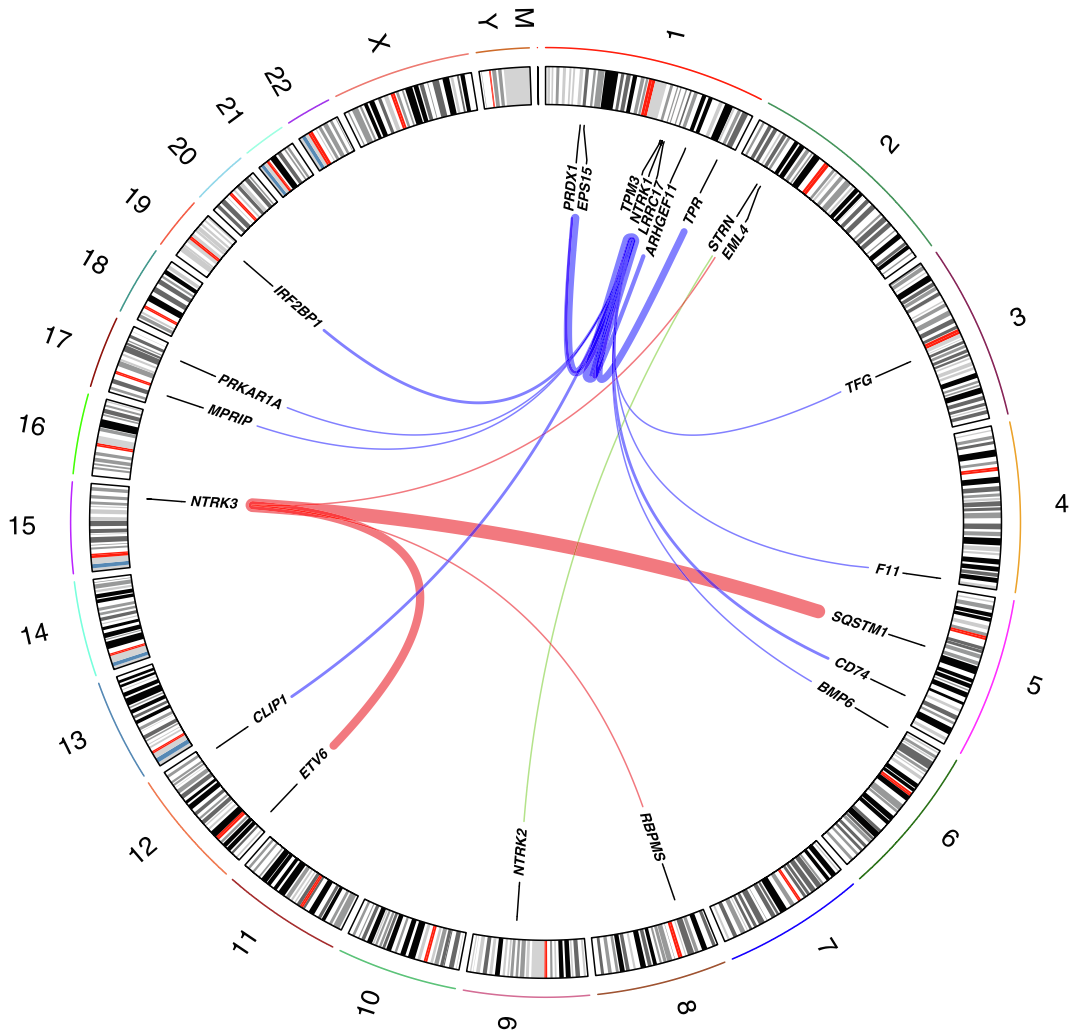

Fig. 1. Circos plot representing the most frequently observed fusions with *NTRK* genes in lung cancer [14,16,35,66,83–85]. The thickness of the joining line is directly proportional to the frequency of the specific fusion plotted in a patient cohort obtained pooling together multiple studies characterising *NTRK* fusions in lung cancer [14,16,35,66,83–85]. *NTRK*: neurotrophic tyrosine receptor kinase.

recommend *NTRK* gene fusion testing in advanced solid tumours without known actionable mutations [57]. In line with the discussion above, some of these guidelines recommend using IHC for screening and NGS for confirmatory testing [57].

ESMO guidelines recommend different testing strategies based on fusion prevalence. In high-prevalence cases (applicable to non-lung cancers such as secretory carcinomas and fibrosarcomas), initial testing by FISH, RT-PCR or RNA-based sequencing panels can be performed. In unselected populations where fusions are less common (as is the case with NSCLCs), NGS should be the first choice, keeping in mind that RNA-based NGS can be better at fusion detection than DNA-based NGS. However, in scenarios where NGS is not readily available, IHC can be used as a screening tool [9].

Management of patients while awaiting testing results

In 2020, the American Society of Clinical Oncology conducted a survey to study oncologists' biomarker-testing practices and the impact on treatment decisions [7]. Nearly a quarter of clinicians said that they were concerned about delaying treatment while waiting for test results, and 50% of clinicians were likely to start non-targeted systemic therapy if test results were not available in under 2 weeks [7]. While access to select targeted therapies in particularly regulated environments may be contingent on the receipt or lack of other systemic therapies like chemotherapy, failure to start first-line chemotherapy may result in rapid disease progression and patient decline. In the same survey, two-thirds of clinicians were likely to switch to targeted therapy once molecular testing results returned positive for a fusion; a third opted to continue systemic therapy unless it became intolerable or failed [7].

Some clinicians may choose to start treatment while waiting for test results; however, it is important to consider the possible consequences of these treatments. PD-L1 testing is often performed at diagnosis and a positive result may prompt the use of immunotherapy (either alone or with chemotherapy). The use of immunotherapy should be approached with caution, as oncogene-driven lung cancers, particularly those with fusions, have had historically limited benefit, particularly with single-agent immune checkpoint inhibition [58]. The administration of TKIs after initial treatment with immune checkpoint inhibitors also has potential for toxicity [58,59]. For example, a study of patients with *EGFR*-mutant NSCLC treated with PD-L1 blockade and EGFR TKIs found that PD-L1 blockade followed by treatment with osimertinib was associated with severe immune-related AEs. These AEs were more frequent among patients who had recently received PD-L1 blockade treatment (within the last 3 months) compared with patients who had treatment more than 1 year before [59]. There are currently no data available on the safety of TKI therapy after initial treatment with immune checkpoint inhibitors in *NTRK* gene fusion-positive NSCLC.

Real-world evidence has demonstrated the importance of universal and rapid testing in patients with advanced NSCLC and the impact on

Table 2
Global recommendations for *NTRK* gene fusion testing.

Name of country/organisation/group	Recommendations for biomarker testing in lung cancer	Recommendations for *NTRK* gene fusion testing, if applicable
Multidisciplinary consensus of key Spanish medical societies on optimising the detection of *NTRK* gene alterations in tumours [50]	Molecular screening in lung cancer should include *NTRK* gene fusions If no testing is done for *NTRK* and testing does not show alterations in *KRAS*, *NRAS*, *BRAF*, *EGFR*, *ALK*, *ROS1* or *RET*, it is still important to evaluate for *NTRK* since these fusions are usually exclusive to the other alterations	
Belgian expert consensus for tumour-agnostic treatment of *NTRK* gene fusion-drive solid tumours with larotrectinib [79]	Recommend including *NTRK* gene fusions in the testing panel for tumour types that already undergo broad genomic testing via DNA and RNA-NGS at the time of diagnosis (such as advanced lung adenocarcinoma and squamous cell)	Recommend that ideally all locally advanced and metastatic solid tumours should be tested for *NTRK* gene fusions in parallel to other actionable oncogenic drivers
Consensus of a Singapore Task Force for recommended testing algorithms for *NTRK* gene fusions in paediatric and selected adult cancers [80]	Recommend NGS testing upfront for *NTRK* gene fusions alongside key oncogenic drivers (*EGFR*, *ALK*, *ROS1*, *MET*, *BRAF*, *PD-L1*)	
Consensus of Japanese medical societies on the diagnosis and use of TRK inhibitors in adult and paediatric patients with *NTRK* fusion-positive advanced solid tumours [81]	Recommendations specific to lung cancer not provided	Do not recommend testing for *NTRK* gene fusions in patients with solid cancers that have genetic alterations that are mutually exclusive with *NTRK* gene fusions Strongly recommend testing for *NTRK* gene fusions for known cancer types in which *NTRK* gene fusions are detected at a high frequency
Canadian consensus for testing and treatment of TRK fusion cancer in paediatric patients [82]	Recommendations specific to lung cancer not provided	Recommend for tumour types with an intermediate or low probability of harbouring an *NTRK* gene fusion, ideally all patients with locally advanced/metastatic disease or those being considered for systemic therapy would be offered a comprehensive RNA-based NGS panel for all known oncogenic drivers, including *NTRK* gene fusions
Expert consensus on diagnosis and treatment of *NTRK* gene fusion solid tumours in China [41]		Recommend that all advanced adult and paediatric solid tumours be tested for *NTRK* gene fusions Recommend a DNA-based NGS panel with the *NTRK*'s intron region covered or whole exome sequencing as the main method for *NTRK* gene fusion detection

NGS: next-generation sequencing; NSCLC: non-small cell lung cancer; *NTRK*: neurotrophic tyrosine receptor kinase; TRK: tropomyosin receptor kinase.

treatment outcomes. The results of a retrospective analysis showed that overall survival was significantly worse in patients with NSCLC that harboured an oncogenic driver who received initial treatment with non-TKI therapy [58]. In an ideal situation, identifying patients who may benefit from targeted treatment as early as possible is critical in maximising benefit and avoiding harm. The results of this retrospective analysis demonstrate the importance of universal and rapid testing in patients with stage IV NSCLC [58].

TRK fusion-targeted therapy

Larotrectinib and entrectinib are two first-generation TRK inhibitors currently approved for the treatment of patients with TRK-fusion solid tumours [2,60]. Both are adenosine triphosphate (ATP)-competitive inhibitors. A kinome inhibition assay on a panel of 255 kinases showed that larotrectinib displayed high selectivity at 1 μmol/L, inhibiting > 95% TRKA, TRKB and TRKC and showed lower inhibition than all other tested kinases. Larotrectinib only displayed additional inhibition of more than 50% for ROS1 and ACK1, while all other kinases were inhibited less than 50%. On the other hand, entrectinib inhibited 75 of the 255 profiled kinases by more than 50% at 1 μmol/L (Fig. 2**A**) [60].

Larotrectinib

Larotrectinib is the first-in-class, highly selective TRK inhibitor approved for adult and paediatric patients with solid tumours that have an *NTRK* gene fusion (without a known acquired resistance mutation), are metastatic or for which surgical resection is likely to result in severe morbidity and have no satisfactory alternative treatments or have progressed following treatment [61]. Larotrectinib has demonstrated activity in TRK fusion lung cancers. In a recent cohort of 30 patients of a median age of 56 years (range 25–81), patients received a median of two prior lines of systemic therapies and most (93%) had adenocarcinomas [62]. In 27 evaluable patients, the overall response rate (ORR) per independent review committee (IRC) assessment was 74% (95% confidence interval [CI] 54–89; Table 3) [62]. The median duration of response (DoR) was 33.9 months (95% CI 9.5–not estimable [NE]) at a median follow-up of 22.9 months. The median progression-free survival (PFS) was 33.0 months (95% CI 11.3–NE) at a median follow-up of 24.7 months (Fig. 2**B**) [62]. Treatment-related AEs (TRAEs) were mostly grade 1 or 2. Five patients experienced a grade 3 TRAE (two each had increased aspartate aminotransferase levels and increased weight; one each had increased alanine aminotransferase levels, myalgia and hypersensitivity). There were no treatment discontinuations due to TRAEs [62].

Entrectinib

Entrectinib is a multi-kinase TRK, ROS1 and ALK inhibitor that is approved for adult and paediatric patients older than 1 month of age

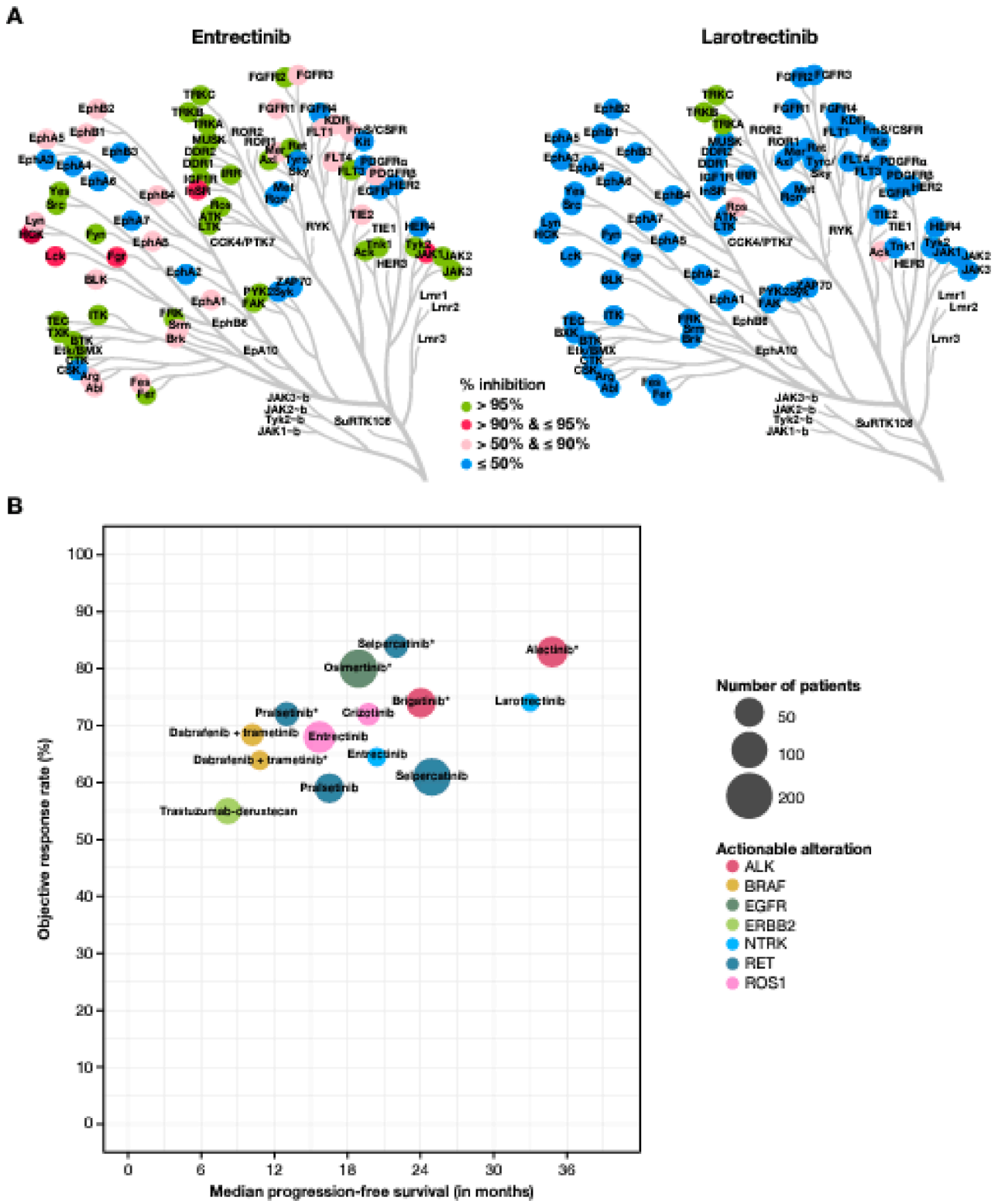

Fig. 2. A) Kinome dendrograms for entrectinib and larotrectinib showing the percentage of kinase activity inhibition for 76 wild-type tyrosine kinases in the presence of 1 μmol/L inhibitor, from Kooijman et al [60]. B) Bubble plot comparing the ORR and PFS of various FDA-approved drugs commonly used in the treatment of NSCLC with oncogenic kinase alterations. Data plotted come from trials that led to the approval of the agent by the regulatory authority. Activity of agents highlighted with (*) comes from treatment-naïve patients, while all other data come from activity in pretreated patients. Diameter of the bubble is directly proportional to the number of patients that participated in the regulatory trial. FDA: U.S. Food and Drug Administration; NSCLC: non-small cell lung cancer; ORR: objective response rate; PFS: progression-free survival.

Table 3
Efficacy of first-generation TRK inhibitors in patients with TRK fusion lung cancer.

	Larotrectinib[†] N = 30 [62]	Entrectinib[‡] N = 31 [64]
ORR, % (95% CI)		
All patients	74 (54–89)	64.5 (45.4–80.8)
Patients with known baseline CNS metastases	Not reported	60.0 (32.3–83.7)
DoR		
Median, months (95% CI)	33.9 (9.5–NE)	27.1 (14.8–29.4)
Median follow-up, months	22.9	Not reported
PFS		
Median, months (95% CI)	33.0 (11.3–NE)	20.8 (13.8–30.4)
Median follow-up, months	24.7	Not reported
OS		
Median, months (95% CI)	39.3 (17.2–NE)	NE
Median follow-up, months	23.1	Not reported

[†]Data cut-off: 20 July 2022.
[‡]Data cut-off: 2 August 2021. CI: confidence interval; CNS: central nervous system; DoR: duration of response; NE: not estimable; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; TRK: tropomyosin receptor kinase.

with solid tumours that have an *NTRK* gene fusion (without a known acquired resistance mutation), are metastatic or for which surgical resection is likely to result in severe morbidity and have progressed following treatment or have no satisfactory alternative therapy [63].

Entrectinib is also active in TRK fusion lung cancers. In a recent cohort of 31 evaluable patients, the median age was 60 years (range 22–88) and 11 patients (35.5%) had two or more prior systemic therapies [64]. In this cohort, 18 patients (58.1%) were current or former smokers and the majority of patients (83.9%) had adenocarcinomas. The ORR per investigator assessment was 64.5% (95% CI 45.4–80.8) for all patients (Table 3). In the 15 evaluable patients with baseline CNS metastases, the ORR was 60% (95% CI 32.3–83.7) [64]. The median DoR was 27.1 months (95% CI 14.8–29.4) and the median PFS was 20.8 months (95% CI 13.8–30.4) [64] (Fig. 2**B**).

TRAEs were mostly grade 1 or 2 and non-serious. TRAEs leading to dose reduction, interruption or discontinuation occurred in 31.4%, 28.6% and 5.7% of patients, respectively [64].

CNS activity

Both larotrectinib and entrectinib have demonstrated activity in the CNS [65]. The pooled analyses of patients with TRK fusion lung cancers treated in larotrectinib and entrectinib registrational trials included patients with baseline CNS metastases [66,67]. A recent pooled analysis of data from two global, multicenter, registrational clinical trials of larotrectinib in patients with TRK-fusion NSCLC showed that, among 10 patients with baseline CNS metastases, the ORR per IRC assessment was 88% (95% CI 47–100) [66]. The intracranial ORR with entrectinib in eight patients with TRK fusion NSCLC with baseline CNS metastases was 63% per blinded independent central review assessment. The median intracranial PFS in this cohort was 8.9 months [67].

Management of AEs associated with TRK inhibition

First-generation TRK inhibitors are well tolerated overall. As reported in earlier datasets, rates of dose interruption and dose discontinuations due to treatment-emergent AEs were 39% and 9% for larotrectinib [61], and 46% and 9% for entrectinib [63], respectively. In more recent studies of larger datasets, rates of dose reduction and dose discontinuation due to TRAEs were not reported and 2% for larotrectinib [68], and 25.6% and 6.5% for entrectinib [69], respectively. Common TRAEs include weight gain, dizziness and withdrawal-associated pain, as well as CNS, gastrointestinal and respiratory symptoms (Fig. 3) [70,71].

Clinical trial experience with larotrectinib and entrectinib have provided guidance for expert recommendations based on AE-management outcomes [70,71]. Weight gain, dizziness, paraesthesias and withdrawal pain could all be considered 'on-target' AEs secondary to the inhibition of TRKA/B/C that play post-developmental

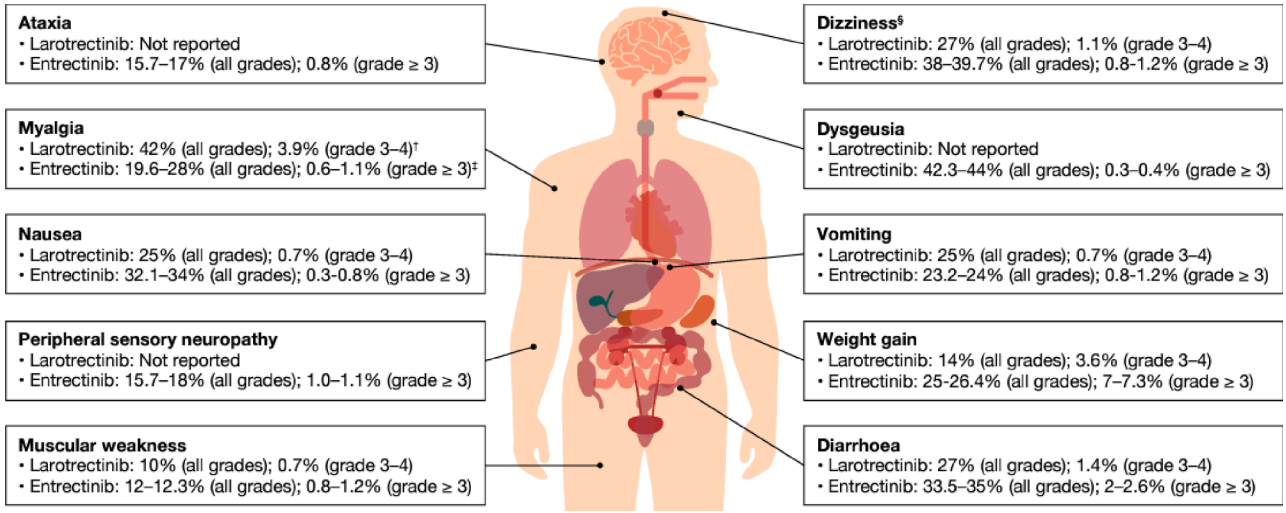

Fig. 3. Frequency and severity of adverse events in patients treated with larotrectinib and entrectinib [61,63,86]. [†]Includes: arthralgia, back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, musculoskeletal stiffness, myalgia, neck pain, non-cardiac chest pain and pain in extremity. [‡]Includes musculoskeletal pain, musculoskeletal chest pain, myalgia and neck pain. [§]Includes dizziness, dizziness postural and vertigo.

roles in the maintenance of the nervous system [13,65,70]. A number of measures can be employed for relief of these symptoms as outlined below and TRK inhibitor dose reduction should be considered in the absence of good symptom control or presence of severe AEs.

'Dizziness' should be appropriately characterised, and dose reduction should be considered for intolerable dizziness unresponsive to pharmacologic management [70,71]. Ataxia (proprioception or vestibular) can be managed using meclizine or scopolamine. Patients should avoid activities that increase the risk of dizziness and should change position slowly [70,71]. Orthostasis can be managed with midodrine or fludrocortisone. Non-pharmacological interventions include avoiding alcohol, caffeine and nicotine; keeping eyes open while showering to avoid dizziness; using a mobility aid if needed; and multidisciplinary care such as physiotherapy and occupational therapy [71].

Monitoring a patient's weight while on TRK inhibitors is advised. Non-pharmacological or pharmacological interventions are available for patients who exceed a clinically meaningful threshold over the ideal body weight [13,70,71]. In a study from Liu et al., most patients treated with exercise and dietary modifications, or pharmacological interventions including glucagon-like peptide 1 analogues, metformin, bupropion, topiramate, sibutramine and phentermine, had minor weight loss or weight stabilisation [70].

Dysesthesias and peripheral sensory neuropathies can be managed with duloxetine. Dysgeusia, a common CNS-related AE, has no pharmacological treatment, so relies on dose interruption and non-pharmacological interventions in moderate-to-severe cases [71].

Withdrawal-associated pain can occur in patients who temporarily or permanently discontinue TRK inhibitor therapy [13,65,70,71]. Non-narcotic and narcotic pain medication can be used during this period, along with a slow taper of the TRK inhibitor [13,70]. In patients who discontinue the drug temporarily, TRK inhibitor reintroduction often results in substantial/complete relief, underscoring how chronic TRK inhibitor therapy may reset one's threshold for feeling pain [70,71].

Acquired TRK inhibitor resistance

Selective evolutionary pressure applied by TRK inhibitor treatment can elicit convergent evolution of both on-target acquired TRK kinase resistance mutations or off-target oncogene dysregulations as an escape mechanism to TRK inhibition. Acquired on-target resistance mutations in the kinase domain are frequent with larotrectinib and entrectinib. These resistance mutations cluster together in three main conserved residue hotspots with similar functions across TRK proteins: the solvent-front, gatekeeper and xDFG residues [13]. Substitutions that result from these mutations occur in areas next to the ATP-binding pocket occupied by the TKI, directly inducing steric clash with the drug or increasing the ATP affinity of the mutant protein [2,13]. In general, on-target resistance mutations should be targeted with next-generation TRK inhibitors that can overcome these resistance mutations [25]. Drugs such as repotrectinib, taletrectinib and paltimatrectinib were designed to bind the ATP pocket of the target kinase and are able to target both wild-type and mutant kinases thanks to their more compact linear or macrocyclic structure [2,65].

Repotrectinib is a next-generation macrocyclic TKI that is selective and highly potent against TRK, ROS1 and ALK. It exhibits activity against a variety of solvent-front mutations both *in vitro* and *in vivo* [72]. In multiple preclinical models, repotrectinib demonstrated potent antiproliferative activity against wild-type fusion proteins involving TRKA, TRKB, TRKC and their corresponding solvent-front mutations in cellular inhibitory assays and xenograft models [72]. Repotrectinib was granted breakthrough therapy designation in October 2021 for patients with advanced solid tumours that have an *NTRK* gene fusion who progressed following treatment with one or two prior TRK inhibitors, with or without prior chemotherapy, and have no satisfactory alternative treatments [73].

Taletrectinib is a next-generation, potent, linear, selective pan-TRK and ROS1 inhibitor that is being investigated in a phase 2 basket study of patients with *NTRK* gene fusions [74]. While presently no clinical data are available on taletrectinib's activity on acquired resistance mutations to first-generation TRK inhibitors, *in vitro* evidence indicates that taletrectinib might be able to overcome some of these mutations [25]. In *in vitro* assays on Ba/F3 cell lines expressing the *TPM3*::*NTRK1* fusion, taletrectinib was, to a degree, able to inhibit solvent-front mutations (G595X), albeit with a slight increase in the half maximal inhibitory concentration (IC_{50}). On the other hand, the xDFG *NTRK* G667C mutation was found to be resistant to taletrectinib, with an IC_{50} of $>$ 300 nM [25,75].

SIM1803-1A is a novel, small molecule pan-TRK/ROS1 dual inhibitor of undisclosed structure that targets both the wild-type and multiple clinical mutations of TRK and ROS1 with a clean selectivity profile [76]. *In vitro* characterisation of this agent showed high potency against wild-type *NTRK1*, as well as against G595R solvent-front mutation and xDFG mutation G667C. Preclinical studies have shown that it is a potent inhibitor with a potentially better safety profile arising from improved kinase selectivity, although no clinical data are yet available [76].

Paltimatrectinib (PBI-200) is a novel, selective, linear, brain-penetrant, next-generation pan-TRK inhibitor. It retains activity against resistance mutations reported in patients receiving first-generation TRK inhibitors [77] like *NTRK1* solvent-front G595R and xDFG G667C mutations. Based on its activity against resistance mutations and its excellent brain penetration, paltimatrectinib holds good potential as a TRK inhibitor, especially for primary brain tumours or brain metastatic lesions that harbour an *NTRK* gene fusion [77].

Off-target resistance to TRK inhibitors is mediated by the acquisition of additional driver genomic alterations that converge to activate the MAPK pathway [2,78]. The use of next-generation TRK inhibitors is not likely to be effective if resistance is due to off-target acquired resistance [25]. *BRAF* V600E mutations, *KRAS* G12D mutations and *MET* amplifications have been identified as the bypass-mediated resistance mechanisms to TRK inhibitors [78]. As is the case for other targeted therapies (*EGFR*, *ALK*, etc.), the optimal treatment for acquired resistance will likely depend on individual analysis of resistance mechanisms and appropriate targeting [25]. Combinations of targeted therapies might be an option for patients with multiple drug-resistance pathways [78]. In the absence of other targetable mutations, or in the presence of a genomic configuration where combination treatment strategies might not be feasible, standard chemotherapy can be an option [25].

Conclusions

NTRK gene fusions are a highly actionable therapeutic target found in NSCLCs. TRK inhibitors have improved outcomes for patients with TRK-fusion cancers, including NSCLCs; therefore, it is important to test all patients with NSCLC for the presence of *NTRK* gene fusions to match patients to targeted therapy. Although there are multiple testing methods available, RNA-based NGS is considered to be the gold standard for detecting *NTRK* gene fusions. First-generation TRK inhibitors are currently approved in a tumour-agnostic fashion. Next-generation drugs with activity against resistance mutations are in development. There are unique TRK inhibitor-related AEs that should be monitored. Delays in identifying and treating these patients with targeted therapy has been shown to have a negative effect on their outcomes. Therefore, it is crucial to test and identify patients who may benefit from targeted treatment as early as possible to maximise the benefits of these treatments.

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