How selecting best therapy for metastatic *NTRK* fusion-positive non-small cell lung cancer?

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Abstract: The tropomyosin receptor kinase (TRK) family of receptor tyrosine kinases has become a focus of clinical interest because the *NTRK* genes (*NTRK1-3*) encoding them have been identified as oncogenic fusion genes in a wide range of different tumor types, including lung cancer. These *NTRK* gene fusions usually occur at a low frequency below 1%, in non-small cell lung cancer (NSCLC) in 0.1–0.2% of the cases and have been reported across a wide range of tumor types. The TRK fusion proteins encoded by such gene fusions have constitutively activated tyrosine kinase domains and constitute actionable targets for tyrosine kinase inhibitors (TKIs). The first generation TRK TKIs larotrectinib and entrectinib have been investigated in clinical phase I and II trials in solid tumors both in adult and pediatric patients and results have demonstrated high response rates that are durable and with generally good tolerability. This has led to approval of these TRK inhibitors by regulatory authorities in the USA, Europe and Japan as tumor agnostic treatment of advanced or recurrent *NTRK* fusion-positive cancers in adult and pediatric patients. With a focus on lung cancer, this review gives a background to *NTRK* fusion genes, presents clinical data for TRK inhibitors and discuss the issue of acquired resistance to TRK inhibition.

Keywords: NTRK; tropomyosin receptor kinase (TRK); fusion; non-small cell lung cancer (NSCLC); inhibitor

Introduction

Lung cancer is one of the most common cancer types with around 2 million new cases diagnosed globally each year and by far the most deadly cancer type with around 1,76 million lung cancer deaths each year in the world (1). With the advent of precision cancer medicine targeting oncogenic drivers the treatment landscape of non-small cell lung cancer (NSCLC) has drastically changed with improved survival and quality-of-life for patients treated with tyrosine kinase inhibitors (TKIs) against various oncogenic genetic aberrations. The identification of gene fusions as oncogenic drivers in cancer in general and in NSCLC in particular has led to important developments of novel diagnostic techniques and therapeutics in these fusion gene positive cancers. Interestingly, in the search of oncogenic fusion genes it has been discovered that many of these occur across other tumor types than lung cancer. In NSCLC, the identification of the gene rearrangement between Echinoderm microtubule-associated protein-like 4 (EML4) and the anaplastic lymphoma kinase (ALK) in a NSCLC patient in 2007 (2) started a new era of treating oncogenic gene fusions in NSCLC with TKIs. Later, rearrangements of the gene encoding ROS1 proto-oncogene receptor tyrosine kinase was identified as a molecular subgroup of NSCLC highly susceptible to the TKI crizotinib (3). Both ALK and ROS1 are now clinically actionable targets tested for and treated with TKIs in clinical routine.

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The tropomyosin receptor kinase (TRK) family of receptor tyrosine kinases (RTKs) has recently become a focus of interest in the clinical setting because the *NTRK* genes encoding them have been identified as oncogenic fusion genes in a wide range of different tumor types, including lung cancer. This review gives a background to *NTRK* genes in cancer and describes the recent clinical developments in targeting *NTRK* fusion gene positive lung cancer.

NTRK genes and TRK receptors

The RTKs TRKA, TRKB and TRKC are transmembrane receptor tyrosine kinases encoded by the neurotrophic TRK (*NTRK*) genes, where TRKA is encoded by *NTRK1* located on chromosome 1q21-q22, TRKB by *NTRK2* located on chromosome 9q22.1 and TRKC by *NTRK3* on chromosome 15q25 (4). Structurally, the TRK receptors consist of an extracellular domain, a transmembrane region and an intracellular part containing the tyrosine kinase domain. The extracellular domain contains a cysteine-rich cluster (C1), three leucine-rich 24-residue repeats (LRR1–3), another cysteine-rich cluster (C2) and two immunoglobulin-like domains (Ig1 and Ig2). TRK receptors are activated by a family of ligands called the neurotrophins that are involved in multiple ways in the development and function of the central nervous system. Of the four neurotrophins identified, Nerve Growth Factor (NGF) binds to TRKA, brain-derived neurotrophic factor (BDNF) and neurotrophin 4 (NT-4) bind to TRKB, and neurotrophin 3 (NT-3) binds to TRKC (5).

Upon ligand binding and receptor dimerization, the TRK receptors undergo autophosphorylation of tyrosine residues in the intracellular domain leading to activation of downstream signaling pathways, including Ras/Raf/MAPK, PI3K/Akt/mTOR and PLCγ pathways. In this way, the TRK receptors regulate different cellular processes such as proliferation, survival and differentiation. The TRK receptor signaling pathways play crucial roles in neuronal differentiation and development and in maintaining normal neuronal homeostasis. Their activation has been shown to be involved in synapse formation and plasticity as well as axon and dendrite formation, with implications in memory function, nociception and proprioception (6). Neurotrophins and their TRK receptors also have roles in non-neuronal tissue including skeletal tissue, vasculature, and the immune system (7-9). In human lung tissue, neurotrophins and their receptors have been showed to be expressed on a protein level in different components of the lung, including bronchial epithelial cells and alveolar cells, suggesting a role in the regulation of normal lung function (10).

Discovery of NTRK gene fusions in cancer

Constitutive activation of the TRK receptors can occur through different chromosomal rearrangements, including inversions, deletions or translocations, resulting in in-frame fusions of the C-terminal tyrosine kinase domain of the *NTRK* genes with an N-terminal fusion partner. Generally, the fusion eliminates the ligand binding site, resulting in ligand-independent dimerization and phosphorylation of the receptors (*Figure 1*). The majority of the 5′ fusion partners described contains a gene sequence encoding one or more dimerization domains that mediate this ligand-independent activation. The first *NTRK* fusion gene observed was in a patient with colorectal cancer in 1986 involving the tropomyosin 3 gene (*TPM3*) and *NTRK1* (11). Later on other *NTRK* fusions have been discovered in colorectal cancer, including *LMNA-NTRK1* and *SCYL3-NTRK1* (12,13). Infantile fibrosarcoma, which is a rare malignant tumor of fibroblasts representing <1% of pediatric cancers, has been characterized by an *ETV6-NTRK3* fusion gene in around 70% of the cases, involving a translocation of chromosomes 12 and 15 (14). The same fusion gene has also been reported as commonly occurring in the rare secretory carcinomas of the breast (15) and salivary gland (16). *NTRK* fusion genes have also been described in multiple other tumor types, including in papillary thyroid carcinoma, especially radiation-associated, lung cancer, gliomas, other sarcomas, inflammatory myofibroblastic tumors, melanocytic tumors, and intrahepatic cholangiocarcinomas (5). Up to now, more than 80 different fusion partners to *NTRK* have been identified in many different adult and pediatric tumor types. Generally, *NTRK* fusions are found at low frequencies in common tumor types (commonly <1%) whereas in some rare cancers they occur at a high frequency (>80%). Fusion genes involving *NTRK1* and *NTRK3* appear to occur more commonly, including in thyroid cancer, whereas *NTRK2* fusions occur in some cancer types, such as gliomas and sarcomas (17).

TRK receptors/neurotrophins and NTRK fusion genes in lung cancer

Neurotrophins and their TRK receptors have been implicated in lung cancer in several studies. Preclinical
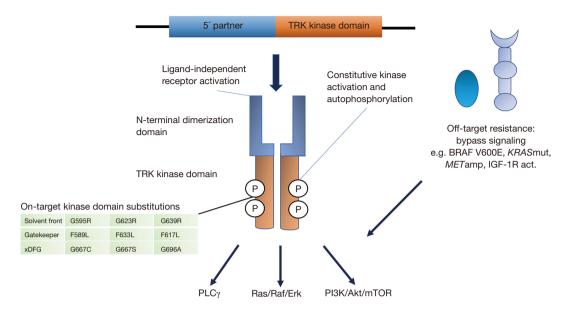
Figure 1 Constitutive activation of the TRK receptors occurs through different chromosomal rearrangements resulting in in-frame fusions of the C-terminal tyrosine kinase domain of the *NTRK* genes with an N-terminal fusion partner. The fusion results in ligand-independent dimerisation and autophosphorylation of the receptors, leading to constitutive activation of downstream signaling pathways, including Ras/Raf/Erk, PI3K/Akt/mTOR and PLCγ pathways. Acquired resistance to TRK inhibitors are mediated by either on-target substitutions in the kinase domain (in solvent front, gatekeeper region or xDFG motif) or off-target activation of bypass signaling pathways. *KRAS*mut, *KRAS* mutation; *MET*amp, *MET* amplification; IGF-1R act, IGF-1R activation.

studies in lung cancer cell lines and a mouse model identified BDNF and TrkB to be important for migration and metastasis, where knockdown of TrkB in human lung cancer cell lines significantly decreased migration and metastasis. TrkB protein expression in patient samples was also found to be correlated with distant metastasis (18). Another study demonstrated that TrkB and BDNF protein expression determined by immunohistochemistry (IHC) was significantly correlated with clinical outcomes, where TrkB-positive tumors had significantly worse disease-free survival and overall survival compared to TrkB-negative tumors, and that co-expression of TrkB and BDNF resulted in a poorer prognosis compared with overexpression of either protein alone (19). Odate *et al.* investigated the protein expressions of TrkB and BDNF analyzed by IHC in surgical samples of lung cancer (n=104) and expressions were significantly higher in neuroendocrine tumors (NETs) compared with non-NETs, in particular in large cell neuroendocrine carcinomas (LCNEC) (20).

Rearrangements of *NTRK* occur in a small subgroup of lung cancer (<1%). The first *NTRK* gene rearrangements described in lung cancer was in 2013 in a fraction of

NSCLC patients with adenocarcinoma histology. In this study, targeted next generation sequencing (NGS) was performed in tumor samples from 36 patients without any known genetic alterations using standard clinical assays. *NTRK1* fusion genes were observed in 3/91 (3.3%) of patients, including two novel fusion partners, myosin phosphatase Rho-interacting protein gene (*MPRIP*) and *CD74*, respectively. In addition, a novel *TMP53-NTRK2* rearrangement was also reported (21). In a phase I study of entrectinib in *NTRK*-rearranged solid tumors, 1,378 NSCLC patients were screened and one patient with lung adenocarcinoma harbored a novel *SQSTM1-NTRK1* fusion gene and one patient had a previously described *TPM3-NTRK1* rearrangement, resulting in an *NTRK* fusion gene incidence of 0.1% (22). *NTRK* fusions involving *NTRK2* has also been reported with a *TRIM24-NTRK2* gene fusion identified in a lung adenocarcinoma in RNAseq data from the Cancer Genome Atlas (17). In a study by Farago *et al.*, 11 NSCLC patients harboring *NTRK* gene fusions verified by NGS were described (23). *NTRK* fusions involved *NTRK1* in 7 cases and *NTRK3* in 4 cases, the latter including fusion partners *ETV6* and *SQSTM1*. The patients

described in this cohort had no other concurrent oncogenic drivers identified, 55% were male, median age at diagnosis was 47.6 years and smoking status with a median pack year history of 0 (range, 0–58). Regarding histology, nine cases were adenocarcinoma, one was squamous cell carcinoma and one neuroendocrine carcinoma. In 4,872 consecutively screened NSCLC patients, the estimated frequency of *NTRK* fusions in NSCLC was 0.23%. The discrepancy of reported incidence of *NTRK* fusions in NSCLC between different studies is likely reflecting the different patient populations and sample sizes, but the incidence is likely to be low in the range of 0.1–0.2%.

Methods for detection of NTRK fusion genes

There are several different methods for the diagnosis of *NTRK* fusions (24). These methods include DNA-based or RNA-based NGS, fluorescence in-situ hybridization (FISH) or IHC (25). Clinical testing of *NTRK* fusions has been dominated by NGS. However, not all NGS platforms are optimized to identify *NTRK* fusions and especially the detection of *NTRK2* and *NTRK3* may be complicated by the presence of large intronic regions. Targeted RNA sequencing can be a complementary method to DNA-based NGS assays and enables detection of both known and unknown upstream gene partners. Besides tissue-based testing of DNA or RNA, *NTRK* fusions can potentially be detected using blood-based cell-free DNA (cfDNA) testing. FISH and RT-PCR have been successfully used in the clinic to detect oncogenic fusions in solid tumors and are especially useful for tumor types with a high prevalence of known *NTRK* fusions, such as *ETV6-NTRK3* in infantile fibrosarcomas, secretory breast carcinoma, and mammary analogue secretory carcinoma (MASC). Advantages of FISH include the low amount of material needed (a few unstained slides) and that it can be performed relatively quickly within a few days. IHC to examine protein expression is another method that can be used for the detection of TRK overexpression reflecting the potential presence of an *NTRK* fusion. IHC has several advantages: it is commonly used in clinical pathology laboratories, it is inexpensive, requires limited amount of material and has a fast turnaround time. The sensitivity and specificity of pan-TRK antibodies have shown to be acceptable with a sensitivity ranging from 75% to more than 96% and a specificity ranging from 92% to 100%, however these being variable depending on *NTRK* fusion type and tumor type (26,27). With limited resources and/or access to NGS, using IHC as a screening tool for

NTRK fusions is a valid option, but confirming positive IHC stainings with nucleic acid-based testing is needed. On the other hand, IHC should be used to confirm protein expression of *NTRK* fusions detected by nucleic acid-based testing since not all *NTRK* fusion genes are expressed and the protein kinase is the pharmacological target (27).

TRK inhibitors in treatment of NTRK-positive cancer including NSCLC

First-generation TRK inhibitors

There are two first generation TRK TKIs, larotrectinib and entrectinib, which potently and selectively inhibit TRKA, TRKB and TRKC, with IC50 values ranging between 5–11 and 1–5 nM, respectively, for TRKA/B/C in *in vitro* assays (28,29). Whereas larotrectinib is a selective inhibitor of TRKA/B/C, entrectinib in addition inhibits ROS1 (IC50 0.2 nM) and ALK (IC50 1.6 nM) (30) (*Table 1*). There is also a group of multi-kinase inhibitors that inhibits the TRK receptors, including inhibitors that are approved for other indications such as crizotinib, cabozantinib, ponatinib and nintedanib, as well as the investigational inhibitors lestaurtinib, altiratinib, foretinib, merestinib, MGCD516, PLX7486, DS-6051b, and TSR-011 (6). These multi-kinase inhibitors have not been well characterized in the clinical setting compared to the more selective TKIs.

Larotrectinib

Larotrectinib has been clinically investigated regarding safety and efficacy in patients harboring *NTRK*-rearranged tumors in three clinical trials; a phase 1 study involving adults, a phase 1–2 study involving children (SCOUT), and a phase 2 study involving adolescents and adults (NAVIGATE) (*Table 2*).

There have been several reports from these studies (28,31). Responses have been reported to occur regardless of tumor type and treatment considered tolerable with the majority of adverse events (93%) being grade 1 or 2. The most common adverse events included anemia (11%), increased liver enzymes (7%), weight increase (7%), and decrease in neutrophil count (7%). Other adverse events reported include fatigue, dizziness, nausea and constipation. Recently, a pooled analysis of the three trials was published with 159 TRK fusion-positive cancer patients (32). Objective response rate was reported to be 79% according to investigator assessment, with 16% CR. Twelve patients with lung cancer were included, 9 of whom (75%) had an

Table 1 Kinase activity of TRK inhibitors in clinical use and under development

Kinase inhibitor: kinase	Larotrectinib	Entrectinib	Selitrectinib	Repotrectinib
TRKA/B/C	+	+	+	+
ROS1		+		+
ALK		+		+
TRKA/B/C on-target mutations			+	+

TRK, tropomyosin receptor kinase.

Table 2 TRK inhibitors in selected clinical studies

Study/author	Treatment	Design	No. of pts.	ORR (%)	PFS (months)	OS (months)	trAEs (% gr.3–5)
Drilon et al. (28)	Larotrectinib	Phase 1/2	55	75	NA	NA	gr.3: 13%, gr.4–5: 0%
Lassen et al. (31)	Larotrectinib	Phase 1/2	122	81	NA	NA	gr.3: 6%+ <1% for fatigue, dizziness, myalgia, gr.4:<1% ALT increase, gr.5: 0%
Hong et al. (32)	Larotrectinib	Phase 1/2	159	79	28.3 (22.1–NE)	44.4 (36.5–NE)	gr.3: 39%, gr.4: 7%, gr.5: 0%
Demetri et al. (33)	Entrectinib	Phase 1/2	54	57.4	11.2 (8.0–14.9)	20.9 (14.9–NE)	gr.3: 37%, gr.4: 1.5%, gr.5: 0%
Doebele et al. (34)	Entrectinib	Phase 1/2	54	57	11.2 (8.0–14.9)	Estimated 21 (14.9–NE)	gr.3: 61%, gr.4: 9%, gr.5: 0%
Hyman et al. (35)	Selitrectinib	Phase I + EAP	29	34	NA	NA	

In brackets for PFS and OS, 95% CI. TRK, tropomyosin receptor kinase; ORR, overall response rate; PFS, progression-free survival; OS, overall survival; NA, not available; EAP, Early Access Program; trAEs, treatment-related adverse events; gr., grade; CI, confidence interval; NE, not estimable.

objective response. There were 12 evaluable patients with brain metastases before enrollment with 9 of them (75%) having a response. Only 3 of the 12 patients with brain metastases had measurable disease at baseline; of these one had a CR, one a PR and one stable disease. The most common grade 3 or 4 larotrectinib-related adverse events were increased alanine aminotransferase (3%), anaemia (2%), and decreased neutrophil count (2%). The most common larotrectinib-related serious adverse events were increased alanine aminotransferase (2/260 patients, <1%), increased aspartate aminotransferase (<1%), and nausea (<1%). No grade 5 AE occurred. A recent update from ESMO 2020 on 14 lung cancer patients (13 with NSCLC and one with small cell lung cancer) reported an ORR of 71% (1 CR, 9 PR) and with a median PFS not reached, estimated PFS rate at 12 months was 69%. The ORR in patients with CNS metastases was 57% (36).

The results from the clinical trials described above lead to the approval of larotrectinib by the Food and Drug Administration (FDA) in November 2018 for adult and pediatric patients with solid tumors that have a *NTRK* gene fusion, that are either metastatic or where surgical resection is likely to result in severe morbidity, and who have no satisfactory alternative treatments or whose cancer has progressed following treatment. A similar approval was granted in July 2019 by the European Medicines Agency (EMA) being the first histology-independent agnostic cancer treatment approved in Europe.

Entrectinib

The clinical trials that have led the clinical development of entrectinib are a phase I trial in adults (ALKA-372-001, Italy), a separate adult phase I trial (STARTRK-1, global), a phase II basket trial (STARTRK-2, including *NTRK1/2/3*, *ROS1* or *ALK* gene fusions), and a phase I/Ib pediatric trial (STARTRK-NG) (*Table 1*). Demetri and colleagues first reported on efficacy in 54 adult patients included in these trials and safety results reported in 355 patients (33). The most common tumor types were sarcomas (24%), lung cancer (19%), mammary analogue secretory carcinoma (13%) and breast cancer (11%). In the safety population, most treatment-related AEs were grade 1–2 and managed

with dose reduction in 27.3%. The most common AEs included dysgeusia, constipation, fatigue, diarrhoea, oedema and dizziness. A recent integrated analysis of three phase 1/2 clinical trials enrolling adult patients with metastatic or locally advanced NTRK fusion-positive solid tumors who received entrectinib was reported (34). These studies are ongoing; NCT02097810 (STARTRK-1), NCT02568267 (STARTRK-2), and EudraCT, 2012-000148-88 (ALKA-372-001). Fifty-four patients were evaluable for efficacy representing ten different tumor types and 19 different histologies. Most patients had a *NTRK1* or *NTRK3* fusion with the most frequently represented gene fusion being *ETV6-NTRK3*, which was identified in 46% of the patients. Thirty-one of 54 patients had an ORR (57%), of which 7% were CRs and 50% PRs. Median duration of response was 10 months and median PFS was 11 months. At data cutoff, the estimated median OS was 21 months (95% CI 14.9 to not estimable). Twelve out of 54 patients (22%) had baseline CNS metastases, as assessed by investigator, with a 50% partial response rate per blinded independent central review. In total, 55% of the brain metastasis patients had an intracranial response (6 out of 11) according to blinded independent review. Safety analysis was reported from two populations, including an NTRK fusion-positive population (68 patients from STARTRK-1, STARTRK-2, and ALKA-372-001 who received at least one dose of entrectinib) and an overall safety-evaluable population (355 patients), including the phase 1 STARTRK-NG study with patients of any tumor type and gene rearrangement who received at least one dose of entrectinib. Consistent with the report from Demetri and colleagues mentioned above, the most common treatment-related AEs in both safety populations were grade 1–2 and reversible. The most common grade 3 or 4 treatment-related AEs in both safety populations were increased weight (10% in the NTRK fusion-positive safety population and in 5% in the overall safety-evaluable population) and anaemia (12% and 5%, respectively). The most common serious treatment-related AEs were nervous system disorders (4% and 3%, respectively) and 4% of patients in both safety populations discontinued entrectinib due to treatment-related adverse events. No treatment-related deaths occurred. A recent update on the ALKA-372-001, STARTRK-1 and STARTRK-2 studies with a focus on NSCLC patients (n=13) demonstrated an ORR of 69%, 9 patients had baseline CNS metastases showing an equally good ORR of 67% (37).

Based on the clinical trial data described above, FDA granted accelerated approval to entrectinib in August 2019 for adults and pediatric patients 12 years of age and older with solid tumors that have a *NTRK* gene fusion without a known acquired resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity, and have progressed following treatment or have no satisfactory standard therapy. Entrectinib has also received approval in Japan in June 2019 with the same indication as defined by FDA.

TRK inhibitor resistance and next generation TRK inhibitors

On-target resistance

Despite high clinical activity of TRK inhibitors, acquired resistance to treatment is a major clinical issue and cases of resistance to entrectinib and larotrectinib have been reported. This resistance can be mediated by on-target and off-target mechanisms (*Figure 1*). On-target resistance occurs via mutations in the NTRK kinase domain of the oncogenic fusion gene resulting in amino acid substitutions that involve three major regions: the solvent front, the gatekeeper residue or the activation loop xDFG motif. These alterations cause resistance by steric hindrance, altering the conformation of the kinase domain or changing ATP-binding affinity. The first reported case of acquired resistance to TRK inhibition occurred in a patient with *LMNA-NTRK1* rearranged colorectal cancer after 4 months of entrectinib treatment (38). Sequencing of cfDNA revealed two mutations that affected the kinase domain and resulted in the two substitutions G595R and G667C. The G595R substitution is located in the solvent front region of the TRK kinase domain (paralogous to the ALK G1202R and ROS1 G2032R substitutions) and G667C is located in the 'x' position of the xDFG motif in the activation segment of the TRKA kinase domain (paralogous to the ALK G1269A). Another solvent front substitution, G623R in TRKC, was reported in a patient with mammary analogue secretory carcinoma (MASC) progressing on entrectinib and this substitution is estimated to sterically interfere with drug binding (39). Furthermore, gatekeeper substitutions have been identified, including TRKA-F589L, TRKB-F633L and TRKC-F617L that are paralogous to ALK-L1196M and ROS1-L2026M (40). Substitutions involving the xDFG site of TRKA (G667S) and TRKC (G696A) have been identified in patients progressing on larotrectinib (28).

Off-target resistance

Off-target resistance to TRK TKIs may develop in a similar

way as for other TKI treatments against oncogenic-driven cancer. This resistance is mediated by the activation of various parallel bypass signaling pathways circumventing the blockade by the on-target TKI. Recently, Cocco *et al*. reported on off-target resistance mechanisms in a series of TRK inhibitor-treated patients and patient-derived models mediated by genomic alterations that converged to activate the mitogen-activated protein kinase (MAPK) pathway (41). These alterations included a BRAF V600E mutation, *KRAS* mutations and a *MET* amplification. MAPK pathway-directed targeted therapy, alone or in combination with TRK inhibition, managed to re-establish disease control. Another off-target resistance mechanism identified in cell line models is the activation of the insulin growth factor receptor type 1 (IGF-1R) pathway (42).

Next generation TRK inhibitors

Selitrectinib (LOXO-195, BAY2731954) and repotrectinib (TPX-0005) are the two major second generation TRK inhibitors in clinical development (*Table 1*) and that are able to inhibit most on-target NTRK resistance mutations while maintaining activity against wild-type TRKA/B/C. Both these inhibitors have demonstrated *in vitro* activity in the low nanomolar concentration range against both wild-type TRKA/B/C and many of the resistant TRK mutants (*Table 2*).

Clinical data on selitrectinib was reported from patients enrolled in a phase I clinical trial and a FDA expanded access program (35). All the patients, both adult and pediatric, had previously been treated with at least one first-generation TRK targeted agent. Twenty-five of the total 29 patients were evaluable for response and ten of the patients (34%) had a confirmed complete or partial response. Nine of 20 patients (45%) whose tumors had become resistant by secondary on-target *NTRK* gene mutations had a complete or partial response. None of the three patients whose tumors had become resistant by TRK-independent mechanisms responded to selitrectinib. The safety and efficacy of selitrectinib is currently being investigated in a phase I/II trial in adult and pediatric patients with *NTRK*-rearranged cancers after prior treatment with a different TRK inhibitor (NCT03215511).

The clinical activity of repotrectinib has been reported from an ongoing phase I/II study of (TRIDENT-1; NCT03093116), in which a patient with MASC and acquired resistance to entrectinib mediated by a solvent front mutation (TRKA-G623E) had a response to repotrectinib (43). Another patient with a larotrectinib-resistant cholangiocarcinoma with LMNA-TRKA G595R and F589L

mutations also experienced a tumor regression (44).

Conclusions

NTRK fusions are oncogenic drivers that have been identified in a wide variety of adult and pediatric cancers, in some cancers highly enriched and in others occurring at a low frequency, including in common cancers like lung cancer. Treatment with a first-generation TRK inhibitor results in high response rates irrespective of tumor type, fusion type and age. However, acquired resistance to TRK inhibitors is a clinical issue and occurs via two different mechanisms; on-target resistance mediated by TRK kinase domain substitutions or off-target activation of bypass signaling pathways. On-target resistance may be overcome with next generation TRK inhibitors that are currently undergoing clinical trials and sequential TRK targeted therapy may therefore be a treatment option for some *NTRK* fusion-positive patients. There is still scarce data about the optimal treatment sequence of TRK inhibitors in relation to other therapies, including chemotherapy and immune checkpoint inhibitors, and also the efficacy of these other treatments in *NTRK* fusion-positive NSCLC. In parallel, there is data indicating that immune checkpoint inhibitors in other oncogenic-driven lung tumors, including *epidermal growth factor receptor* (*EGFR*)-mutated and *ALK*-rearranged NSCLC have limited efficacy (45). Considering the high response rates of TRK inhibitors also in first line, and the scarcity of data for other therapies, it can be recommended that TRK inhibitors are used as first-line therapy if the *NTRK* fusion is discovered prior to the start of first-line systemic therapy. Upon progression, initial systemic therapy options used for other non-oncogenic-driven NSCLC can applied or alternatively inclusion into clinical trials with next generation TRK-inhibitors. If the *NTRK* fusion is discovered during first-line systemic therapy there is an option to complete the ongoing systemic therapy or interrupt the ongoing treatment and switch to a TRK-inhibitor depending on the clinical situation. These recommendations are also in line with the FDA and EMA approvals and the National Comprehensive Cancer Network (NCCN) guidelines. Generally, TRK inhibitors demonstrate a good tolerance but in some cases on-target adverse events may occur, including neurological symptoms. Ongoing and future studies will shed further light on the role and activity of TRK inhibitors in different patient groups, relation to other treatments, sequencing of TRK inhibitors as well as resistance mechanisms.

Acknowledgments

Footnote

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