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Insights About NTRK Gene Fusion Testing and TRK Inhibitors Comparative Effectiveness for Best Clinical Practice

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***Abstract*—** Precision medicine aims to identify the genetic landscapes of each patient's cancer to maximize effectiveness and minimize toxicity to normal cells. Due to the efficacy of tropomyosin receptor kinase (TRK) inhibitor therapy, it is currently clinically recommended to identify patients with neurotrophic tropomyosin receptor kinase (NTRK) fusion-driven cancer. In this article we aim to provide perceptions to enhance best clinical practices about NTRK gene fusion testing and monitoring parameters for the approved TRK inhibitors as well as its comparative effectiveness based on previously published articles and guidelines. Identification of NTRK gene fusion may be attained using different methods based on histology and molecular findings. The possible methods for detection are immunohistochemistry, fluorescence in situ hybridization, reverse transcriptase polymerase chain reaction and next generation sequencing. FDA approved two TRK inhibitors Larotrectinib and Entrectinib. Based on management guidelines, oncologists have one opportunity to decide which TRK inhibitor to choose for patients. There is no direct comparison in clinical trials and Larotrectinib versus Entrectinib comparative efficacy still unclear. In addition, cross-trial comparisons are susceptible to potential biases. Indirect comparative efficacy of Larotrectinib (Vitrakvi) versus Entrectinib (Rozlytrek) was conducted by Jesus Garcia-Foncillas and colleagues. The matching-adjusted indirect comparison (MAIC) to compare the 2 agents was utilized. They assumed this model would aid to balance baseline characteristics and facilitate cross-trial comparisons. The published findings propose favorable efficacy for Larotrectinib regarding OS and PFS and comparable ORR and safety profiles compared to Entrectinib in treating TRK fusion positive cancer. In conclusion, further research should re-assess the comparative effectiveness of both TRK inhibitors as long-term survival data mature and increased number of patients are treated. Furthermore, data with longer follow up times will further enlighten this comparison.

Keywords: NTRK Gene Fusion, TRK Inhibitors Comparative Effectiveness, IHC-FISH-NGS, Larotrectinib versus Entrectinib, Non-Small Cell Lung Cancer (NSCLC), Colorectal Cancer (CRC).

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1. Introduction

Understanding the cell death regulation process and survival is crucial for the development of therapeutic strategies for cancer management. Accordingly, targeting growth factors has particular consequence. Nerve growth factor (NGF) is a neurotrophic factor responsible for the differentiation and survival of both sympathetic and sensory neurons as well as selective population of cholinergic neurons [1]. Several novel members of the NGF family of neurotrophins, that consists of nerve growth factor itself, neurotrophins and brain derived neurotrophic factor have been isolated recently. Tropomyosin receptor kinase (TRK) is a receptor in the tyrosine kinase family that is activated by neurotrophins. Their signaling receptors have been recognized as the TRK family of tyrosine protein kinase, hence facilitating the dissection of the signaling pathways which is responsible for mediating their trophic properties. TRK family members play vital roles in nervous system development through cell proliferation regulation, differentiation, apoptosis, and survival of neurons in the peripheral as well as central nervous system. TRK receptors are expressed in the nervous system and also in several other non-neuronal cell types and tissue, including bone, monocytes, lung and pancreatic B cells [2].

There are three members of the TRK family members have been described namely neurotrophic tropomyosin receptor kinase NTRK1(also known as TRKA), NTRK2 (also known as TRKB), and NTRK3 (also known as (TRKC), encoded by NTRK1, NTRK2, NTRK3 genes, respectively. The oncogenic fusions occur when any of the three NTRK genes fuse with any of a number of N-terminal partners [3-6].

NTRK fusions have been found in many tumors in adults and pediatric patients. These types of cancers can be grouped into two categories according to the frequency at which these fusions are detected. First rare types of cancer highly enriched for NTRK fusions e.g., secretory breast carcinoma, congenital mesoblastic nephroma and infantile fibrosarcoma with a prevalence of > 90%. These are known as high prevalence tumors. Second, other cancer types in which NTRK fusions are found in a much lower frequency (5-25% or < 5%). These are known as low prevalence tumors. NTRK fusions can be detected in < 5% (predominantly <1%) of pancreatic

adenocarcinomas, head and neck, lung, breast, squamous cell, bile duct, renal cell carcinoma, colorectal, melanomas, primary brain tumors of adulthood (e.g., astrocytomas and glioblastomas), and non-GIST soft-tissue sarcomas. While Spitzoid neoplasms, papillary thyroid cancers, gastrointestinal stromal tumors (GIST) lacking canonical KIT, PDGFRA, or RAS alterations, and certain pediatric gliomas are among the tumor types that have been shown to harbor NTRK fusions with frequencies of 5–25% [5-7].

2. MECHANISM OF ONCOGENESIS

TRKA, TRKB and TRKC are transmembrane proteins that include the TRK receptor family. TRKA is encoded by the NTRK1 gene positioned on chromosome 1q21-q22. TRKB is encoded by the NTRK2 gene located on chromosome 9q22.1. TRKC is encoded by the NTRK3 gene placed on chromosome 15q21[8-11]. The TRK receptors are triggered by a family of four proteins called neurotrophins. Each of the four neurotrophins have specificity for a particular TRK and bind to it with high affinity. NGF binds to TRKA, both neurotrophin 4(NT-4) and brain derived neurotrophic factor (BDNF) binds to TRKB, and neurotrophin 3 (NT-3) binds to TRKC. NT-3 can bind to all three TRK receptors, but its highest affinity is for TRKC and is considered its sole ligand [10]. The TRK signaling pathway is initiated when neurotrophin binding to TRK receptors at the cell surface causes the formation of receptor dimers. The dimerized receptor autophosphorylates specific tyrosine residues in the kinase domain activation loop [Y676, Y680 and Y681 in TRKA in addition to the corresponding residues in TRKB and TRKC] [12]. This phosphorylation is essential for activation of the TRK receptor leading to subsequent phosphorylation of another tyrosine residues (Y496 and Y791 in TRKA). This enables docking of cytoplasmic adaptors and enzymes, that in turn drives a variety of downstream signaling pathways. The binding of TRKA by NGF causes activation of the RAS/MAPK pathway, leading to increased cellular proliferation and growth via ERK signaling. Neurotrophic binding to TRKB results in activation of the RAS-ERK, PI3K and PLCγ pathway, resulting in neuronal differentiation and survival. TRKC binding to NT-3 lead to preferential activation of the PI3K/AKT pathway, preventing apoptosis and increasing cell survival [11]. In NTRK gene fusion events, the 3′ region of the NTRK gene is joined with the 5′ end of a fusion partner gene, either by intrachromosomal or interchromosomal rearrangement. The subsequent fusion gene encodes a protein containing the N-terminus of the fusion partner linked to the TRK protein C-terminus as well as the catalytic tyrosine kinase domain. The majority of characterized NTRK gene fusions contain a 5′ partner gene sequence encoding one or more dimerization domains. These domains facilitate the corresponding tyrosine kinase activity, leading to conferring ligand-independent oncogenic potential through uninterrupted downstream signaling messages, promoting cell proliferation and survival [13].

3. METHODS FOR DETECTION OF NTRK FUSION

Precision medicine aims to categorize the genetic features of each patient's cancer to optimize effectiveness while reducing toxicity to normal cells. Due to the efficacy of TRK inhibitor therapy, it is currently essential to efficiently classify patients with NTRK fusion-driven cancer. Precise identification may be accomplished using several methods based on histology and other molecular findings. The following are the possible methods for detection.

3.1 Immunohistochemistry

Immunohistochemistry is the most common tool used to enable the detection of TRK overexpression as a surrogate for the potential presence of an NTRK fusions due to several advantages. It is easy to implement and validate, inexpensive, have a rapid turnaround time, does not require advanced experience, and require one unstained slide per probe examined. The clone that is most often studied and used is clone EPR17341. Its sensitivity ranges from 75% to 96.7% while specificity ranges from 92% to 100%. Recent studies shown the staining intensity to be variable and the staining pattern correlates with fusion pattern. This explains the wide range in sensitivity mentioned above. Accordingly, sensitivity of NTRK3 fusions was 79%, this led to possible false negatives reports mainly in NTRK3 fusion. While the sensitivity of NTRK1 and NTRK2 fusions was 96% and 100% respectively. In addition, specificity is variable according to tumor type. The specificity reaches 100% in carcinomas of the lung, colon, thyroid, biliary tract and pancreas, while it is less in breast and salivary gland carcinomas as cytoplasmic staining can occasionally be seen. Specificity is even lower in sarcomas, particularly those with neural or smooth muscle differentiation as wild-type TRK protein is physiologically expressed in neural and smooth muscle tissue. Tumor types with a >20% rate of TRK fusion positivity (e.g., congenital mesoblastic nephroma, CMN) are candidate for testing using IHC [5-7, 14].

3.2 Fluorescence in situ hybridization (FISH)

FISH has good sensitivity and specificity and often used as the gold standard for assessing for the presence of chromosomal abnormalities and has been successfully used especially for tumor histology with a high prevalence of NTRK fusions involving recurrent partners (MASC, infantile fibrosarcoma, secretory breast carcinoma, and cellular or mixed congenital mesoblastic nephromas). FISH can be performed relatively quickly and available in several laboratories. It requires one unstained slide per probe examined. A marketable break-apart probe is offered for the ETV6 gene. In cases histologically suggestive of ETV6-NTRK3 fusions e.g., infantile fibrosarcoma, secretory carcinoma of the salivary gland, congenital mesoblastic nephroma and breast, this testing might be useful to confirm the translocation. considering fusions in other cancers can include any of the NTRK genes and any of a number of partners through either balanced or unbalanced translocation or large deletions. Only examining the ETV6 gene would miss many oncogenic NTRK fusions. Therefore, break-apart probes for the three NTRK genes have been used to identify fusions. FISH in setting as e.g., FISH break-apart tests generally cannot identify the upstream fusion partner [5-7,15,16].

3.3 Reverse transcriptase polymerase chain reaction (RT-PCR)

Because of the number of different fusion partners and breakpoints involved, the utility of RT-PCR for individual fusion transcripts is limited and has been used in the past mainly to detect canonical ETV6-NTRK3 fusions. Although this method may demonstrate difficulty to obtain direct evidence of a fusion, RT-PCR might be used to examine expression differences of the 5′ versus the 3′ ends of a gene, as this associated with the presence of a translocation. For NTRK, which is not expressed in most normal tissues, the 3′ kinase domain would be transcribed at a much higher level than the 5′ extracellular domain in tumor tissue that harbors an NTRK fusion [5-7,17].

3.4 Next generation sequencing (NGS)

There are two types of NGS, DNA based and RNA based. In case of DNA based NGS, tumor DNA is extracted from formalin fixed paraffin embedded (FFPE) tissue and then sequenced to investigate whether specific alterations are present in the tumor. The sensitivity of DNA-based NGS suffers in case fusion breakpoints include long intronic regions that cannot be covered by hybridization capture probes. Because of the above-mentioned issues coverage of the NTRK3 introns and fusions involving NTRK3 other than ETV6 are not covered by this assay [5-7,18].

Disadvantage of DNA-based NGS is that upon detection of novel structural variants, it can be difficult to determine if such an incident results in a functional expressed fusion. In these cases, RNA-based NGS can be carried out. Another disadvantage includes turnaround time which is significantly longer than IHC or FISH and that more materials is required for testing. While a major plus of DNA-based NGS testing is the interrogation of many genomic events. This led to simultaneous direct assessment of point mutations, copy number variants, indels and tumor mutation burden as well as DNA-level gene fusions. This method is also effective for monitoring patients with NTRK fusions for development of resistance mutations. Using DNA-based NGS to monitor for tumor evolution is useful in patients with NTRK fusion-positive cancers eligible to be treated with TRK inhibitor therapy [5-7,18].

Targeted RNA sequencing can serve as a complementary method to DNA-based NGS assays. Anchored multiplex PCR, a unidirectional targeted RNA sequencing approach that allows for the detection of both known and unknown upstream gene partners of varying lengths, is one example. The custom panel covers fusions involving the kinase domains of the following genes: ALK, BRAF, EGFR, ERBB2, ERBB4, FGFR1, FGFR2, FGFR3, KIT, MET, NTRK1, NTRK2, NTRK3, RET, and ROS1. Tumors tested involved cases with a high suspicion of fusion based on outside testing results or morphology e.g. infantile fibrosarcoma, congenital mesoblastic nephroma, or secretory carcinomas of the breast or salivary gland), and cases including tumor types usually enriched in MAPK driver alterations such as lung adenocarcinoma, colon adenocarcinoma, pancreas adenocarcinoma, that were negative for MAPK driver alterations (i.e., BRAF p.V600E, KRAS/NRAS/EGFR hotspot) on MSK-IMPACT testing [5-18].

RNA-based sequencing presents many advantages compared to DNA. The introns being spliced out in the RNA this removes the technical limitations of intronic coverage. Moreover, detection of RNA-level fusions offers evidence that they are functionally transcribed. In addition, analysis of the spliced sequence can determine if the protein would be translated and in-frame. While in case of the RNA of low tumor purity samples because gene fusions are often highly expressed in these tissues, fusion transcripts can also be detected with high confidence One of the main limitations to working with RNA is its liability and the essential need for adequate quality control because RNA is susceptible to fragmentation and degradation, mainly in older material. Methods to interrogate RNA quality are analysis of RNA fragment size distribution and examining amplification of a housekeeping gene in a quantitative PCR-based assay. For assessing quality of the sequencing assay, one can determine the ratio of RNA reads to DNA reads and examine sequencing coverage and depth for the RNA reads [5-7,19-20]. Figure 1 represents a summary for investigation for NTRK fusions presence.

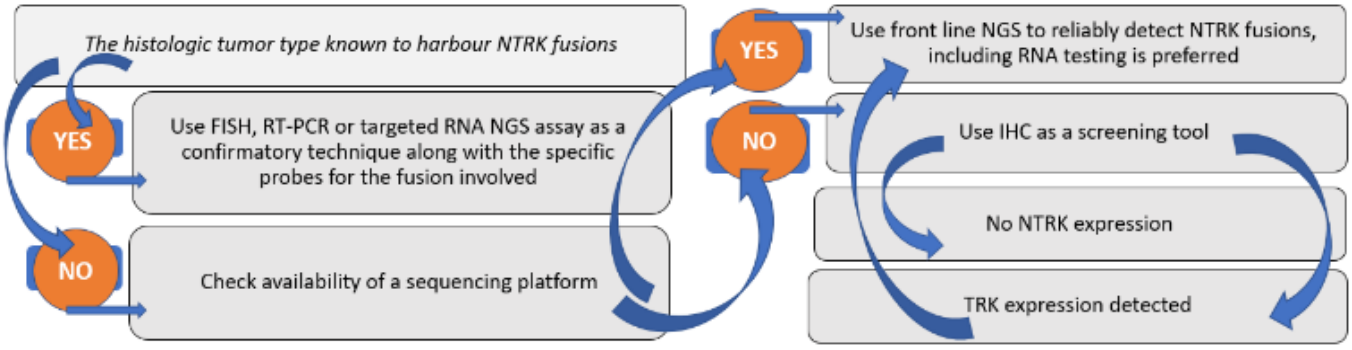

Figure 1: Investigation for NTRK Fusions Presence

4. TRK INHIBITORS APPROVED BY FDA

4.1 Larotrectinib

Larotrectinib is approved on November 2018 for adult and pediatric patients with solid tumors who have NTRK gene fusion without a known acquired resistance mutation, that are either metastatic or surgical resection is not an option due to expected severe morbidity, and no other satisfactory alternative treatment or whose cancer has progressed following treatment. It is a selective inhibitor of TRK A, B and C. FDA approval was based on facts from three multicenter, open-label, single-arm clinical trials LOXO-TRK-14001 (NCT02122913), SCOUT (NCT02637687), and NAVIGATE (NCT02576431). Next generation sequencing (NGS) or fluorescence in situ hybridization (FISH) were used to identify positive NTRK gene fusion status. The major efficacy outcome measures were overall response rate (ORR) and response duration. ORR was 75% (95% CI: 61%, 85%), presented as 22% complete responses and 53% partial responses. While at the time of database lock, median duration of response had not been reached. Response duration was 6 months or longer for 73%, 9 months or longer for 63%, and 12 months or longer for 39% of patients. The safety of Larotrectinib was evaluated in 176 patients enrolled across the three clinical trials, involving 44 pediatric patients. The most common grade 3 or 4 adverse events were increased alanine aminotransferase (3%), anemia (2%) and decreased neutrophil count (2%). The recommended dose for Larotrectinib was 100 mg orally to be taken twice daily for adults. While for pediatric patients, the dose was100 mg/m2 orally twice daily (maximum of 100 mg per dose) [21-23].

4.2 Entrectinib

Entrectinib is approved on August 19, 2019, for adults and pediatric patients 12 years of age and older who have solid tumors with a NTRK gene fusion without a known acquired resistance mutation are metastatic or where resection is likely to result in severe morbidity, and have progressed following treatment or have no standard therapy. It is also approved by FDA for adults with metastatic non-small cell lung cancer (NSCLC) whose tumors are ROS1 positive. Entrectinib inhibits TRK A, B and C and hits for ROS1 and has to activity against ALK at a lesser degree. Efficacy in NTRK-positive tumors was investigated in 54 adult patients in one of three multicenter, single-arm, clinical trials: ALKA, STARTRK-1 (NCT02097810) and STARTRK-2 (NCT02568267); Patients received Entrectinib 600 mg orally once daily. They determined the status of positive NTRK gene fusion using nucleic acid-based tests prior to enrollment [24-25].

Among 54 adult patients, the ORR was 57% (95% CI: 43, 71). Response duration was 6 months or longer for 68% of patients and 12 months or longer for 45% of patients. Median duration of response was 10 months (95% CI 7.1 to not estimate). The most common grade 3 or 4 treatment related adverse events were increase in weight 10% and anemia 12%. Efficacy in ROS1-positive metastatic NSCLC was investigated in 51 adult patients who received Entrectinib in the same three trials. The ORR was 78% (95% CI: 65, 89) and response duration was 12 months or longer for 55% of patients [25-27].

The most serious adverse events were congestive heart failure, hepatotoxicity, hyperuricemia, central nervous system effects, QT interval prolongation, skeletal fractures, and vision disorders. The most common adverse reactions in at least 20% of patients were fatigue, edema, constipation, dysgeusia, dizziness, diarrhea, nausea, dysesthesia, dyspnea, myalgia, cognitive impairment, increased weight, cough, vomiting, pyrexia, arthralgia, and vision disorders [26-28].

5. DOSING AND ADMINISTRATION

Table 1 represent the recommended doses for Larotrectinib and Entrectinib in adult and pediatric patients with NTRK gene fusion positive.

Table 1. The recommended doses for Larotrectinib and Entrectinib in adult and pediatric patients

Larotrectinib	
Dosage forms	25-mg and 100-mg gelatin capsules
	20-mg/mL oral solution
	Both dosage forms may be used interchangeably.
Recommended dose	
Adult & pediatric patients ≥ 28 weeks & BSA ≥ 1.0 m^2	100 mg orally twice daily
Pediatric patients with a BSA < 1.0 m^2	100mg/m^2 orally twice daily.
Entrectinib	
Dosage forms	100-mg and 200-mg capsules
Recommended dose	
Adults: NTRK gene fusion–positive solid tumors and *ROS1*-positive NSCLC	600 mg orally once daily
Pediatrics ≥ 12 years with *NTRK* gene fusion–positive solid tumors, dose is based on BSA	
BSA > 1.50 m^2	600mg once daily
BSA 1.11–1.50 m^2	500mg once daily
BSA 0.91–1.10 m^2	400mg once daily

5.1 Larotrectinib

Larotrectinib can be taken with or without food. It undergoes hepatic metabolism primarily via CYP3A4. Concurrent administration of strong CYP3A4 inhibitors and inducers should be avoided. If coadministration is necessary with strong CYP3A4 inhibitors (e.g., itraconazole), the dose of Larotrectinib should be reduced by 50%. No studies about combination of Larotrectinib with moderate and weak CYP3A4 inhibitors and inducers. The dose of Larotrectinib should be doubled if given in combination with strong CYP3A4 inducers (e.g., rifampin). Renal dose adjustments are not recommended. Pharmacokinetics analysis was not studied with creatinine clearance less than or equal to 60 mL/min. For moderate/severe hepatic impairment (Child-Pugh B and C), it is recommended to reduce the starting dose of Larotrectinib by 50%. The half-life of Larotrectinib is 2.9 hours. The medication is primarily excreted in feces (58%) and 39% in urine (Bayer HealthCare Pharmaceuticals, Inc., 2019) [29].

5.2 Entrectinib

Entrectinib can be taken with or without food until disease progression or intolerable toxicity. The capsules should be swallowed as a whole (Genentech USA, Inc., 2019). Entrectinib is primarily metabolized hepatically via CYP3A4. Therefore, concomitant administration with moderate and strong CYP3A4 inhibitors should be avoided. For patients receiving the 600-mg dose, in case Entrectinib is taken concurrently with moderate and strong CYP3A4 inhibitors, respectively decrease the dose to 200 mg once daily and 100 mg once daily. For moderate and strong CYP3A4 inducers, coadministration with Entrectinib should be avoided. Dose adjustments for mild to moderate renal impairment is not recommended (creatinine clearance 30–89 mL/min). Severe renal impairment (creatinine clearance < 30 mL/min) has not been studied. No dose adjustments are recommended for mild hepatic impairment (total bilirubin ≤ 1.5 × upper limit of normal). Moderate and severe hepatic impairment (total bilirubin > 1.5 x upper limit of normal) have not been studied. The half-life of Entrectinib is 20 hours (40 hours for active metabolite). It is excreted primarily in feces (83%; Genentech USA, Inc., 2019) [29].

6. PATIENT MONITORING AND COUNSELING

Table 2 represents the monitoring parameters and patient counseling information for Larotrectinib and Entrectinib [29].

Table 2. Monitoring parameters and patient counseling information

Larotrectinib	
Monitoring parameters	Monitor liver functions every 2 weeks during the first month, then monthly thereafter.
Patient counseling	Avoid grapefruit and St. John's wort.
	The oral solution should be refrigerated and discarded after 90 days from opening.
	Oral capsules should be swallowed whole, not crushed, or chewed.
	Missed doses should not be taken if they are within 6 hours of the next scheduled dose. If patients vomit a dose, that dose should not be repeated.
	Females of reproductive age and males should be counseled to use effective contraception during Larotrectinib treatment and for 1 week after the final dose.
	Females should avoid breastfeeding during treatment and for 1 week after the final dose
Entrectinib	
Monitoring parameters	Monitor left ventricular ejection fraction at baseline in patients with congestive heart failure risk factors (e.g., hypertension, cigarette use, diabetes, being overweight).
	Monitor liver function tests every 2 weeks during the first month, then monthly thereafter.
	Monitor serum uric acid levels at baseline then as clinically indicated throughout treatment.
	Monitor QT interval and electrolytes at baseline then as clinically indicated throughout treatment.
Patient counseling	Avoid grapefruit.
	Oral capsules should be swallowed as a whole.
	Missed doses should not be taken if they are within 12 hours of the next scheduled dose.
	If a dose is vomited immediately after taking the dose, the patient should repeat the dose.
	Females of reproductive age should be counseled to use effective contraception during Entrectinib treatment and for 5 weeks after the final dose.
	Males with female partners of reproductive potential should use effective contraception during treatment and continue for 12 weeks after the final dose.
	Females should avoid breastfeeding during treatment and for 1 week after the final dose

7. COMPARATIVE EFFECTIVENESS

Based on guidelines [30], oncologists have to decide one TRK inhibitor to select for patients. There is no direct comparison in clinical trials and comparative efficacy still unclear for Larotrectinib (Vitrakvi) versus Entrectinib (Rozlytrek). While cross-trial comparisons are susceptible to potential biases.

7.1 TRK fusion positive solid cancer

Jesus Garcia-Foncillas and colleagues did indirect comparative efficacy of Larotrectinib (Vitrakvi) versus Entrectinib (Rozlytrek) [31]. Researchers utilized matching-adjusted indirect comparison (MAIC) to compare the 2 drugs. They assumed that this type of model would help to balance baseline characteristics and enable cross-trial comparisons in a better way. They matched the patients on baseline characteristics, such as sex, age, race, tumor type (thyroid, sarcoma, salivary, lung, gastrointestinal tumors), metastatic disease, NTRK fusion type, and prior therapy for metastatic disease. They evaluated the outcomes including overall response rate (ORR), complete response (CR) rate, duration of response (DoR), overall survival (OS), progression-free survival (PFS), any serious treatment-related adverse events of grade ≥ 3 (TRAEs), and TRAEs that lead to treatment discontinuation. The MAIC included 74 patients from Entrectinib trials and 117 and 147 patients for the Larotrectinib efficacy and safety populations, respectively. Prior to matching, the median overall survival for Larotrectinib was not reached, whereas the median overall survival for Entrectinib was 23.9 months. After matching, Larotrectinib was associated with a significantly longer median duration of OS than Entrectinib, with a hazard ratio of 0.43 ($P < .05$) and a numerically longer median PFS (hazard ratio = 0.66, $p = 0.07$). ORR was similar for both agents ($p = 0.63$). The CR rate was higher ($p < 0.05$) and the DoR was longer for Larotrectinib ($p < 0.05$). Safety outcomes were comparable and low for both treatments. Results were consistent in sensitivity analyses. These findings suggest favorable efficacy in regard to OS and PFS for Larotrectinib and comparable ORR and safety profiles versus Entrectinib in treating TRK fusion positive cancer [31-33]. **Table 3** represents the effectiveness comparison between Larotrectinib and Entrectinib prior to and after matching in patients with solid tumors.

Table 3. Comparative effectiveness of Larotrectinib versus Entrectinib prior to and after matching

	Prior to matching		After matching	
	Larotrectinib	Entrectinib	Larotrectinib	Entrectinib
Median OS	Not reached	23.9 months	Not reached	
HR	0.43		0.43	
P value	<0.01		<0.05	
Median PFS	33 months	11.2 months	19.3 months	
HR	0.56		0.66	
P value	<0.01		=0.07	
ORR	65%	63.5%	67.3%	
Risk difference (RD)	1.5% (-12.5%, 15.4%)		3.8% (-11.7%, 19.3%)	
P value	0.84		=0.63	
CR	19.7%	6.8%	20.3%	
Risk difference (RD)	12.9% (3.7%, 22.1%)		13.5% (2.9%, 24.1%)	
P value	<0.01		<0.05	
Median DoR	41.5 months	12.9%	32.5 months	
HR	0.33		0.49	
P value	<0.001		<0.05	
Serious TRAEs				
Risk difference (RD)	-4.6%		-3.7%	
P value	0.27		=0.40	
TRAEs leading to discontinuation				
Risk difference (RD)	-3.3%		-3.3%	
P value	=0.18		=0.18	

7.2 TRK fusion positive NSCLC

Joshua A. Roth and colleagues simulated and compared expected life-years and quality-adjusted life-years (QALYs) for both TRK inhibitors. They developed a partitioned survival model to project the long-term comparative effectiveness of Larotrectinib versus Entrectinib in second-line treatment of metastatic NSCLC. Treatment with Larotrectinib and Entrectinib resulted in 5.4 and 1.2 median preprogression life-years and 7.0 and 1.8 median total life-years, respectively. Mean preprogression life-years (QALYs) were 7.5 (5.0) and 1.9 (1.2), and mean total life-years (QALYs) were 9.2 (5.8) and 4.4 (2.4), respectively. Among TRK inhibitors for metastatic NSCLC, Larotrectinib is estimated to provide improved life-year and QALY outcomes versus Entrectinib based on parametric extrapolations of in-trial survival data. The limitations of this analysis are lack of NSCLC-specific data on Entrectinib OS, the small samples of patients with NSCLC, and the cross-trial comparison. [33].

7.3 TRK fusion positive CRC

Kangho Suh and colleagues estimated and compared expected life years (LYs) and quality-adjusted life-years (QALYs) for metastatic TRK fusion CRC patients. They developed a partitioned survival model to project long-term comparative effectiveness of Larotrectinib vs. Entrectinib. Larotrectinib resulted in 2.11 LYs and 1.60 QALYs compared to 0.53 LYs and 0.41 QALYs for Entrectinib. These estimates yielded additional gains for Larotrectinib of 1.58 LYs and 1.19 QALYs against Entrectinib [34].

8. Insights about effectiveness differences

Although both Entrectinib and Larotrectinib are reported to be potent TRK inhibitors, differences in their mechanisms of action may assist to elucidate the differences in their comparative efficacy. Entrectinib is a multi-kinase inhibitor that targets the three TRK proteins in addition to ROS1 and ALK [20]. In contrast, Larotrectinib, which is considered the most specific TRK inhibitor, is a selective inhibitor of the three TRK proteins [5,33]. This difference in their mechanism of action could explain the observed differences in efficacy between the two drugs [30].

9. Future directions

Second generation NTRK inhibitors were developed to overcome the resistance mutations occur with first generation NTRK inhibitors including Larotrectinib and Entrectinib. The 2nd generation NTRK inhibitors have smaller molecular weight and compact macrocyclic structure compared to first generation molecule. Currently there are ongoing trials on Repotrectinib (TPX-0005), Selitrectinib (LOXO-195), and Taletrectinib (DS-6051b/AB-106) [35]. 2nd generation NTRK inhibitors might be a promising option after failure to the 1st generation NTRK inhibitors. Results of the ongoing trials will prove otherwise.

10. Conclusion

Future studies should re-evaluate the comparative effectiveness of both TRK inhibitors as more patients are treated and long-term survival data mature. Furthermore, additional data with longer follow up times will further enlighten this comparison.

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