Clinical outcomes of patients with neurotrophic tyrosine receptor kinase (*NTRK*) gene fusion cancer treated with non-tropomyosin receptor kinase inhibitors: a systematic literature review

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BACKGROUND

- For patients with tumors that harbor neurotrophic tyrosine receptor kinase (*NTRK*) gene fusions, tropomyosin receptor kinase inhibitors (TRKis) provide an effective treatment option that confers a durable response rate (RR), as demonstrated in several single-arm trials.[1-6]
- Larotrectinib is an oral, highly selective, purpose-built TRKi that directly targets tropomyosin receptor kinases, a family of signaling proteins that play an important role in cellular communication and tumor growth. Larotrectinib is a first-in-class, highly selective, central nervous system-active TRK inhibitor approved by the US Food and Drug Administration and European Medicines Agency, and in 48 countries worldwide, for adult and pediatric patients with TRK fusion cancer.[7] However, data of clinical effectiveness of non-TRKi therapies in patients that harbor *NTRK* gene fusions is very limited.

AIMS

- This systematic literature review (SLR) investigated the clinical efficacy and real-world effectiveness of non-TRKi therapies in patients with *NTRK* fusion-positive solid tumors. Outcomes of interest were overall response rate (ORR), progression-free survival (PFS), and overall survival (OS). Eligible non-TRKi therapies were any systemic anticancer therapy, including chemotherapy, targeted medicine (eg, vascular endothelial growth factor inhibitors), and immunotherapy. Larotrectinib, entrectinib, repotrectinib, any investigational therapies targeting TRK kinase and local/reginal therapies, such as surgical treatment, were excluded.

METHODS

- MEDLINE and Embase (via Ovid.com) were searched from database inception to October 26, 2021. Additional grey literature sources, including relevant conferences (European Society for Medical Oncology, American Association for Cancer Research) from 2020 and 2021 were also searched. There was no restriction on language, timeframe, or geography. Search terms included *NTRK*, overall survival, progression-free survival, and overall response; the search used controlled vocabulary terms (Medical Subject Headings) in addition to free-text terms. The SLR followed PRISMA guidelines with scope defined using PICOS criteria (Population, Intervention, Comparators, Outcomes, Study design).
- Literature screening was performed by a single reviewer at the title/abstract phase. Records selected for full-text screening were screened by 2 independent reviewers. The inclusion and exclusion criteria are shown in **Table 1**.

RESULTS

- A total of 2,390 records were screened; 10 studies (total of 454 patients) met the inclusion criteria (**Figure 1**), all of which were conducted in the real-world setting.
- Nine of the included studies were retrospective analyses of real-world outcomes data among patients who had undergone genetic profiling.[8-16] One study was an analysis of prior real-world systemic therapy among patients enrolled in a single-arm trial of entrectinib.[17]
- Tumor types varied considerably; the most common were lung, colorectal, breast, and sarcoma. Two studies included only lung cancer patients,[12,13] while the other 8 studies included a wide range of tumor types (**Table 2**).
- For those studies reporting PFS, the mean or median PFS ranged from 2.1 to 13.6 months (**Figure 2**), except for 1 outlier study among patients with thyroid cancer that reported a median PFS of 196.5 months with >15 years of follow-up due to study design and sample size.
- Four studies reported median OS (ranging from 10.1 to 18 months across the 4 studies) but different definitions of OS were used (eg, time from last line of therapy, time from diagnosis of metastatic disease).
- Two studies reported an ORR for *NTRK* patients with several tumor types. In a study of locally advanced or metastatic cancer, ORR ranged from 7.7% to 15.8%. In another study that included localized, stage I to II cancers of various tumor types, the ORR ranged from 11.1% in people treated with immunotherapy alone to 62.5% in people treated with chemotherapy alone (**Figure 3**); the data were not reported separately for different tumor types.

SUMMARY/CONCLUSION

- Clinical effectiveness data for *NTRK* fusion cancers treated with non-TRKi therapies are sparse. Very few (N=10) studies were identified in the literature, all of which were studies conducted in the real-world setting.
- Detailed information on patient characteristics (eg, disease stage, tumor types, line of therapy) and treatments were largely missing across the included studies.
- The included studies provide some data about effectiveness of standard of care that may allow inference about treatment effect of non-TRKi therapies, however, they are limited in small sample size, heterogeneity in patient populations, different study designs/analyses, and lack of details of treatments. The general trend of data across different outcome endpoints needs to be considered further in treatment decision making. Other treatment options that target oncogenic drivers such as TRKi therapies should be considered.
- Adverse events were not included as outcomes of interest. These data in the real world setting are usually not clean or reliably collected, due to various definitions and inclusion frames across sites or hospitals.
- Response data identified in this review were assessed by the treating physician and recorded on the electronic case report form. The approach to assessing response is different from standard measure using Response Evaluation Criteria in Solid Tumors (RECIST). The measurement difference needs to be considered when interpreting the response data and comparing with ORR reported in clinical trials.
- Further study of effectiveness of non-TRKi therapies in the real world with more detailed clinical and treatment information is warranted to provide a benchmark for evaluation of the clinical value of TRKi.

Table 1. Inclusion and exclusion criteria

	Inclusion criteria	Exclusion criteria
Population	Patients (pediatrics and adults) with *NTRK* fusion-positive solid tumors (also described as *NTRK* rearrangement)	Tumors other than *NTRK* fusion-positive solid tumors
Interventions	Any/all treatments that do not specifically target TRK fusions	Treatment with larotrectinib, entrectinib, reoptrectinib, any investigational therapies targeting TRK kinase, or surgical procedures only
Comparators	Any/all treatments that do not specifically target TRK fusions	
Outcomes	• Response rate • Progression-free survival • Overall survival	Outcomes other than those specified
Study design	• Randomized controlled trials • Non-randomized interventional studies • Observational studies • Any relevant published systematic literature reviews and meta-analyses for hand-searching of the reference lists	• Case series (<5 patients); case reports • Letters, editorials, commentaries, and opinions • Preclinical and in vitro studies

Key: *NTRK* – neurotrophic tyrosine receptor kinase.

Table 2. Characteristics of included studies

Author, year	Data source	Study design	Tumor type	Disease stage	Intervention	Line of therapy	Sample size*	Efficacy outcome
Bazhenova, 2021[8]	Flatiron Health-Foundation clinico-genomic database	Retrospective	Colorectal, salivary gland, lung, and sarcomas	NR	Chemotherapy	NR	27 adults	OS
Krebs, 2021[17]	Phase 2 single-arm trial (STARTRK-2)		Colorectal, pancreatic, neuroendocrine, gynecological, cholangiocarcinoma, upper gastrointestinal tract, neuroblastoma, sarcoma, non-small cell lung, MASC, thyroid	III-IV (metastatic/ locally advanced)	Chemotherapy, targeted therapy, immunotherapy, monoclonal antibody, hormone therapy	1 to ≥3	51 adults	ORR
Liu, 2020[12]	Single hospital		Lung	III-IV	Targeted therapy, chemo-therapy, immunotherapy, anti-angiogenic therapy, EGFR TKI	NR	28 (NR)	PFS
Niu, 2020[13]	Data compiled from a study of ICI treatment and the Genomic Data Commons portal		Lung adenocarcinoma	NR	ICIs	NR	16 (NR)	OS
Rosen, 2020[14]	Memorial Sloan Kettering		Salivary, sarcoma, thyroid, colon, lung, melanoma, pancreatic, breast, and glioma	Localized stage I-III to metastatic stage IV	Chemotherapy, immunotherapy	1	51 adults & children†	ORR, PFS
Zhu, 2022[16]	MD Anderson Cancer Center		Breast, thyroid, colon, and pancreatic	I-IV	Unclear (not TRK inhibitors)	NR	25 adults & children†	PFS
Santi, 2021[15]	Hartwig Medical Foundation clinico-genomic database		Breast, colorectum, head and neck, lung, pancreas, prostate, skin, urothelial tract	Metastatic	Unclear (not TRK inhibitors)	≤2: 65.2% <2: 34.8%	23 adults	OS
Demetri, 2021[10]	Flatiron Health-Foundation clinico-genomic database		Uterine, biliary, stomach, endometrial, cancer of unknown primary, breast, salivary gland	Locally advanced/ metastatic	Unclear (not TRK inhibitors)	0-2: 71.4% ≥3: 10.7% Unknown: 17.9%	28 adults	OS
Bridgewater, 2021[9]	100,000 Genomes Project		Childhood: brain and central nervous system; childhood: other; upper gastrointestinal; hepatopancreatobiliary; sarcoma; adult glioma; colorectal; breast; bladder; renal; lung	I-IV	Unclear (not TRK inhibitors)	NR	18 children	OS
Dufresne, 2021[11]	NeTSarc database, RNASarc molecular screening program, and routine practice		Gastrointestinal stromal tumor, liposarcoma, leiomyosarcoma, undifferentiated pleomorphic sarcoma, uterine sarcoma	Metastatic	Unclear (not TRK inhibitors)	NR	5 adults & children†	OS

*Adult/pediatric population. †Data not reported separately.
Key: EGFR – epidermal growth factor receptor; ICI – immune checkpoint inhibitor; MASC – mammary analogue secretory carcinoma; NR – not reported; ORR – overall response rate; OS – overall survival; PFS – progression-free survival; TKI – tyrosine kinase inhibitor; TRK – tyrosine receptor kinase.
Note: Same patients may be included in multiple studies.

Figure 1. PRISMA flow diagram of literature search and selection

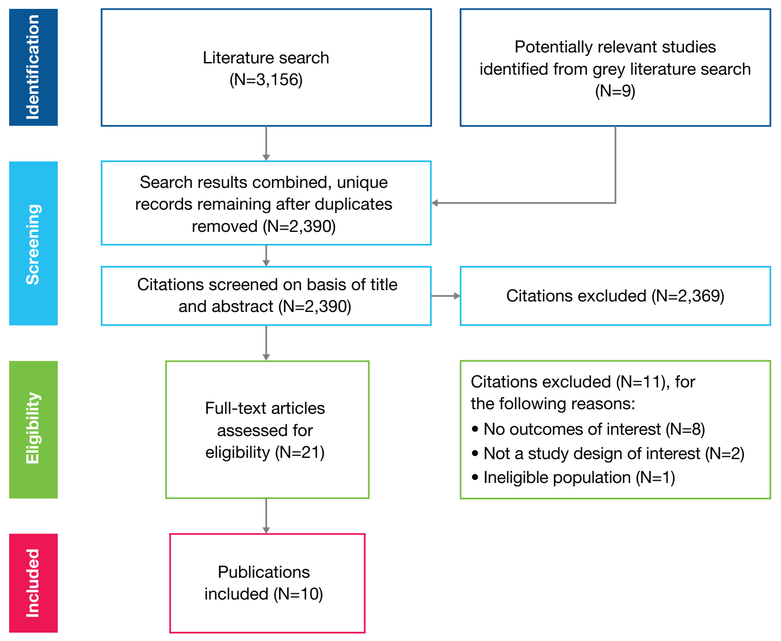
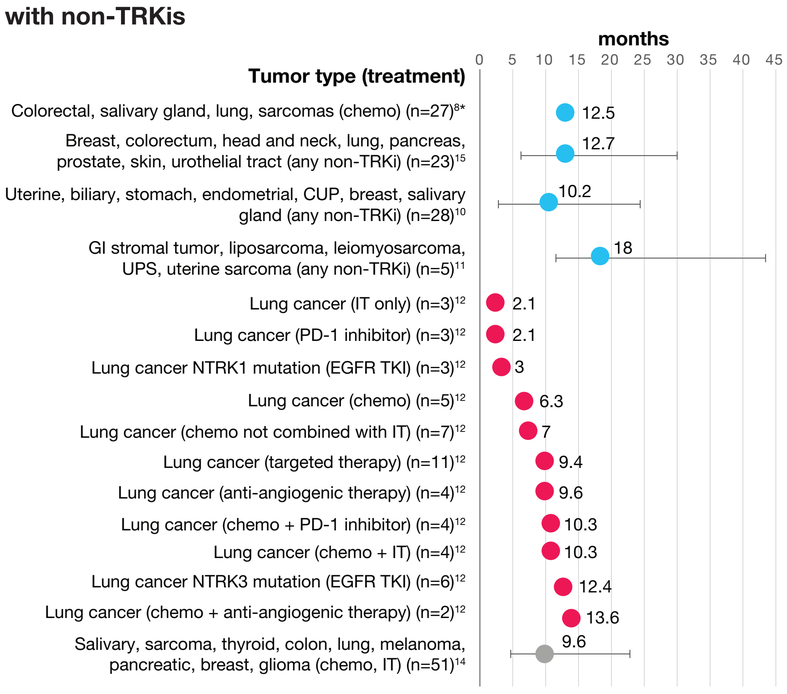
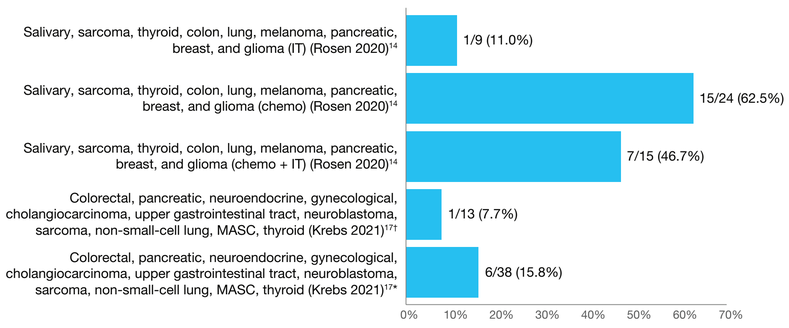


Figure 2. OS and PFS in patients with *NTRK* gene fusions treated with non-TRKis



*95% CI: 9.5, not estimated
Key: CI – confidence interval; CUP – cancer of unknown primary; EGFR – epidermal growth factor receptor; GI – gastrointestinal; IT – immunotherapy; *NTRK* – neurotrophic tyrosine receptor kinase; OS – overall survival; PD-1 – programmed cell death protein 1; PFS – progression-free survival; SD – standard deviation; TRKi – tyrosine kinase inhibitor; UPS – undifferentiated pleomorphic sarcoma.

Figure 3. Overall response rate in patients with *NTRK* gene fusions treated with non-TRKis



*Treatment: Chemotherapy, targeted therapy, IT, monoclonal antibody, hormone therapy. Patients with progression on prior therapy. †Treatment: Chemotherapy, targeted therapy, IT, monoclonal antibody, hormone therapy. Patients with no progression on prior therapy.
Key: IT – immunotherapy; MASC – mammary analogue secretory carcinoma; *NTRK* – neurotrophic tyrosine receptor kinase; TRKi – tyrosine kinase inhibitor.

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