Cancer Association of South Africa (CANSA)

Fact Sheet
on
Tropomyosin Receptor Kinase (TRK) Fusion Cancer

Introduction

The tropomyosin receptor kinase (TRK) family of receptor tyrosine kinases are encoded by NTRK genes and have a role in the development and normal functioning of the nervous system.

[Picture Credit: TRK Fusion Cancer]

Since the discovery of an oncogenic NTRK gene fusion in colorectal cancer in 1986, over 80 different fusion partner genes have been identified in a wide array of adult and paediatric tumours, providing actionable targets for targeted therapy. This review describes the normal function and physiology of TRK receptors and the biology behind NTRK gene fusions and how they act as oncogenic drivers in cancer. Finally, an overview of the incidence and prevalence of NTRK gene fusions in various types of cancers is discussed.

Tropomyosin Receptor Kinase (TRK) Fusion Cancer

Some cancers are caused by specific changes in genes. Genes carry instructions for proteins in cells and an abnormal change to the genes can lead to an alteration of the proteins, which can cause uncontrolled cell growth and formation of a cancerous tumour.

One type of genetically-driven cancer is called tropomyosin receptor kinase (TRK) fusion cancer.

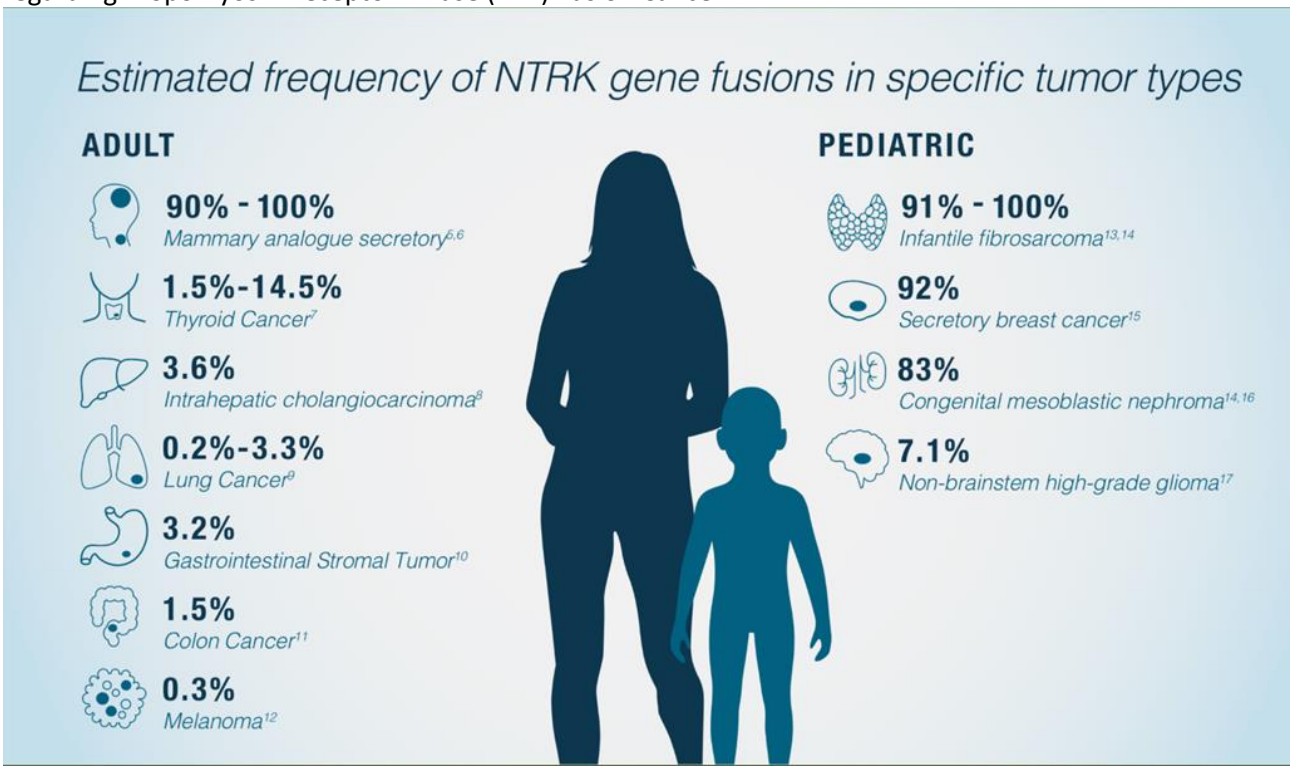
Neurotrophic tyrosine receptor kinase (*NTRK*) genes provide instructions for TRK proteins. When an *NTRK* gene joins or "fuses" with an unrelated gene, it starts to produce an altered TRK fusion protein. This TRK fusion protein becomes active and causes a cancerous tumour to grow.

TRK fusion cancer is a very unique and rare disease and is defined by this specific gene alteration. The cancer is not related to a certain type of tissue or the age of the patient; it can occur anywhere in the body, in both children and in adults.

Researched and Authored by Prof Michael C Herbst
[D Litt et Phil (Health Studies); D N Ed; M Art et Scien; B A Cur; Dip Occupational Health; Dip Genetic Counselling; Dip Audiometry and Noise Measurement; Diagnostic Radiographer; Medical Ethicist]
Approved by Ms Elize Joubert, Chief Executive Officer [BA Social Work (cum laude); MA Social Work]

Incidence of Tropomyosin Receptor Kinase (TRK) Fusion Cancer

The outdated National Cancer Registry (2016), known for under reporting, does not provide any information regarding Tropomyosin Receptor Kinase (TRK) Fusion Cancer.



Diagnosis of Tropomyosin Receptor Kinase (TRK) Fusion Cancer

Only specific genomic tests can detect *NTRK* gene fusions, the underlying cause of TRK fusion cancer. By testing patients and finding out what is driving their cancer, doctors could target the root of the disease. It is important that high-quality genomic testing that looks for actionable targets becomes part of routine clinical practice so patients have the chance to benefit from therapies that selectively inhibit the oncogenic driver that causes their cancer.

Penault-Llorca, F., Rudzinski, E.R. & Sepulveda, A. 2019.

"The neurotrophic tyrosine receptor kinase (*NTRK*) gene family encodes three tropomyosin receptor kinases (TRKA, TRKB, TRKC) that contribute to central and peripheral nervous system development and function. *NTRK* gene fusions are oncogenic drivers of various adult and paediatric tumours. Several methods have been used to detect *NTRK* gene fusions including immunohistochemistry, fluorescence in situ hybridisation, reverse transcriptase polymerase chain reaction, and DNA- or RNA-based next-generation sequencing. For patients with TRK fusion cancer, TRK inhibition is an important therapeutic target. Following the FDA approval of the selective TRK inhibitor, larotrectinib, as well as the ongoing development of multi-kinase inhibitors with activity in TRK fusion cancer, testing for *NTRK* gene fusions should become part of the standard diagnostic process. In this review we discuss the biology of *NTRK* gene fusions, and we present a testing algorithm to aid detection of these gene fusions in clinical practice and guide treatment decisions."

Treatment of Tropomyosin Receptor Kinase (TRK) Fusion Cancer

The treatment of solid tumours is dramatically changing in recent years thanks to the enhancement of molecular diagnostic technologies leading to identification of an increasing number of specific actionable oncogenic abnormalities such as gene activating point mutations, in-frame insertions/deletions and amplification or rearrangements. The concept of precision medicine consists in the accomplishment of therapy individualised to each tumour by exploiting these alterations as predictive biomarkers as well as targets of therapy. Neurotrophic tropomyosin receptor kinase (*NTRK*) gene rearrangements have recently emerged as targets for cancer therapy, because novel compounds have been developed that are selective inhibitors of the constitutively active fusion proteins that arise from these molecular alterations. Developments in this field are being aided by next generation sequencing methods as tools for unbiased gene fusion discovery. In this article, we review the role of *NTRK* gene fusions across several tumour histologies, and the promises and challenges of targeting such genetic alterations for cancer therapy.

Wong, D., Yip, S. & Sorensen, P.H. 2019.

NTRK gene fusions affecting the tropomyosin receptor kinase (TRK) protein family have been found to be oncogenic drivers in a broad range of cancers. Small molecule inhibitors targeting TRK activity, such as the recently Food and Drug Administration-approved agent larotrectinib (Vitrakvi®), have shown promising efficacy and safety data in the treatment of patients with TRK fusion cancers. *NTRK* gene fusions can be detected using several different approaches, including fluorescent in situ hybridization, reverse transcription polymerase chain reaction, immunohistochemistry, next-generation sequencing, and ribonucleic acid-based multiplexed assays. Identifying patients with cancers that harbor *NTRK* gene fusions will optimize treatment outcomes by providing targeted precision therapy.

Solomon, J.P., Benayed, R., Hechtman, J.F. & Ladany, M. 2019.

"Due to the efficacy of tropomyosin receptor kinase (TRK) inhibitor therapy and the recent Food and Drug Administration approval of larotrectinib, it is now clinically important to accurately and efficiently identify patients with neurotrophic TRK (*NTRK*) fusion-driven cancer. These oncogenic fusions occur when the kinase domain of *NTRK1*, *NTRK2* or *NTRK3* fuse with any of a number of N-terminal partners. *NTRK* fusions are characteristic of a few rare types of cancer, such as secretory carcinoma of the breast or salivary gland and infantile fibrosarcoma, but they are also infrequently seen in some common cancers, such as melanoma, glioma and carcinomas of the thyroid, lung and colon. There are multiple methods for identifying *NTRK* fusions, including pan-TRK immunohistochemistry, fluorescence *in situ* hybridisation and sequencing methods, and the advantages and drawbacks of each are reviewed here. While testing algorithms will obviously depend on availability of various testing modalities and economic considerations for each individual laboratory, we propose triaging specimens based on histology and other molecular findings to most efficiently identify tumours harbouring these treatable oncogenic fusions."

Federman, N. & McDermott, R. 2019.

Introduction: Detecting oncogenic drivers across multiple cancers has brought about a shift toward a more targeted therapeutic approach. Neurotrophic tyrosine receptor kinase (*NTRK*) gene fusions are genomic rearrangements containing the kinase domain of one of three tropomyosin receptor kinases (TRK) and a dimerization domain contributed by another gene, generating fusion proteins, which are oncogenic drivers, targetable with TRK inhibitors. Larotrectinib is a first-in-class TRK inhibitor, granted accelerated FDA approval for treating TRK fusion cancer. This breakthrough indication across cancer subtypes and ages, from infancy through adulthood, highlights the need to understand the heterogeneous patient population and cancer types studied in larotrectinib clinical trials.

Areas covered: We provide a narrative review of preclinical, pharmacokinetic, efficacy, and safety data for larotrectinib from three clinical trials that led to regulatory approval.

Expert opinion: Larotrectinib elicits impressive responses in most patients with TRK fusion cancer, regardless of tumor type and age. Treatment is well tolerated with a low rate of treatment-emergent grade 3-4 adverse events, dose reductions and discontinuations due to adverse events, and recent findings indicate patient-reported improvement in quality of life. This highlights the importance of early testing for *NTRK* gene fusions in cancers that may harbor them, even if rare.

About Clinical Trials

Clinical trials are research studies that involve people. They are conducted under controlled conditions. Only about 10% of all drugs started in human clinical trials become an approved drug.

Clinical trials include:

- Trials to test effectiveness of new treatments
- Trials to test new ways of using current treatments
- Tests new interventions that may lower the risk of developing certain types of cancers
- Tests to find new ways of screening for cancer

The South African National Clinical Trials Register provides the public with updated information on clinical trials on human participants being conducted in South Africa. The Register provides information on the purpose of the clinical trial; who can participate, where the trial is located, and contact details.

For additional information, please visit: www.sanctr.gov.za/

Medical Disclaimer

This Fact Sheet is intended to provide general information only and, as such, should not be considered as a substitute for advice, medically or otherwise, covering any specific situation. Users should seek appropriate advice before taking or refraining from taking any action in reliance on any information contained in this Fact Sheet. So far as permissible by law, the Cancer Association of South Africa (CANSA) does not accept any liability to any person (or his/her dependants/estate/heirs) relating to the use of any information contained in this Fact Sheet.

Whilst the Cancer Association of South Africa (CANSA) has taken every precaution in compiling this Fact Sheet, neither it, nor any contributor(s) to this Fact Sheet can be held responsible for any action (or the lack thereof) taken by any person or organisation wherever they shall be based, as a result, direct or otherwise, of information contained in, or accessed through, this Fact Sheet.

Sources and References Consulted and/or Utilised

Amatu, A., Sartore-Bianchi, A., Bencardino, K., Pizzutilo, E.G., Tosi, F. & Siena, S. 2019. Tropomyosin Receptor Kinase (TRK) Biology and the role of NTRK gene fusion in Cancer. Ann Oncol. 2019 Nov 1;30(Suppl_8):viii5-viii15. doi: 10.1093/annonc/mdz383.

Federman, N. & McDermott, R. 2019. Larotrectinib, a highly selective tropomyosin receptor kinase (TRK) inhibitor for the treatment of TRL fusion cancer. *Expert Rev Clin Pharmacol*. 2019 Oct;12(10):931-939. doi: 10.1080/17512433.2019.1661775. Epub 2019 Sep 10.

Penault-Llorca, F., Rudzinski, E.R. & Sepulveda, A. 2019. Testing algorithm for identification of patents wth TRK fusion cancer. *J Clin Pathol*. 2019 Jul;72(7):460-467. doi: 10.1136/jclinpath-2018-205679. Epub 2019 May 9.

Solomon, J.P., Benayed, R., Hechtman, J.F. & Ladany, M. 2019. Identifying patients with NTRK fusion cancer. *Ann Oncol*.. 2019 Nov; 30(Suppl 8): viii16–viii22. Published online 2019 Nov 18. doi: 10.1093/annonc/mdz384

TRK Fusion Cancer
https://pharma.bayer.com/trk-fusion-cancer
https://esmoopen.bmj.com/content/1/2/e000023

TRK Fusion Cancer Picture
https://pharma.bayer.com/trk-fusion-cancer

Wong, D., Yip, S. & Sorensen, P.H. 2019. Methods of identifying patients with tropomyosin receptor kinase (TRK) fusion cancer. *Pathology & Oncology Research*, 2019.