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.

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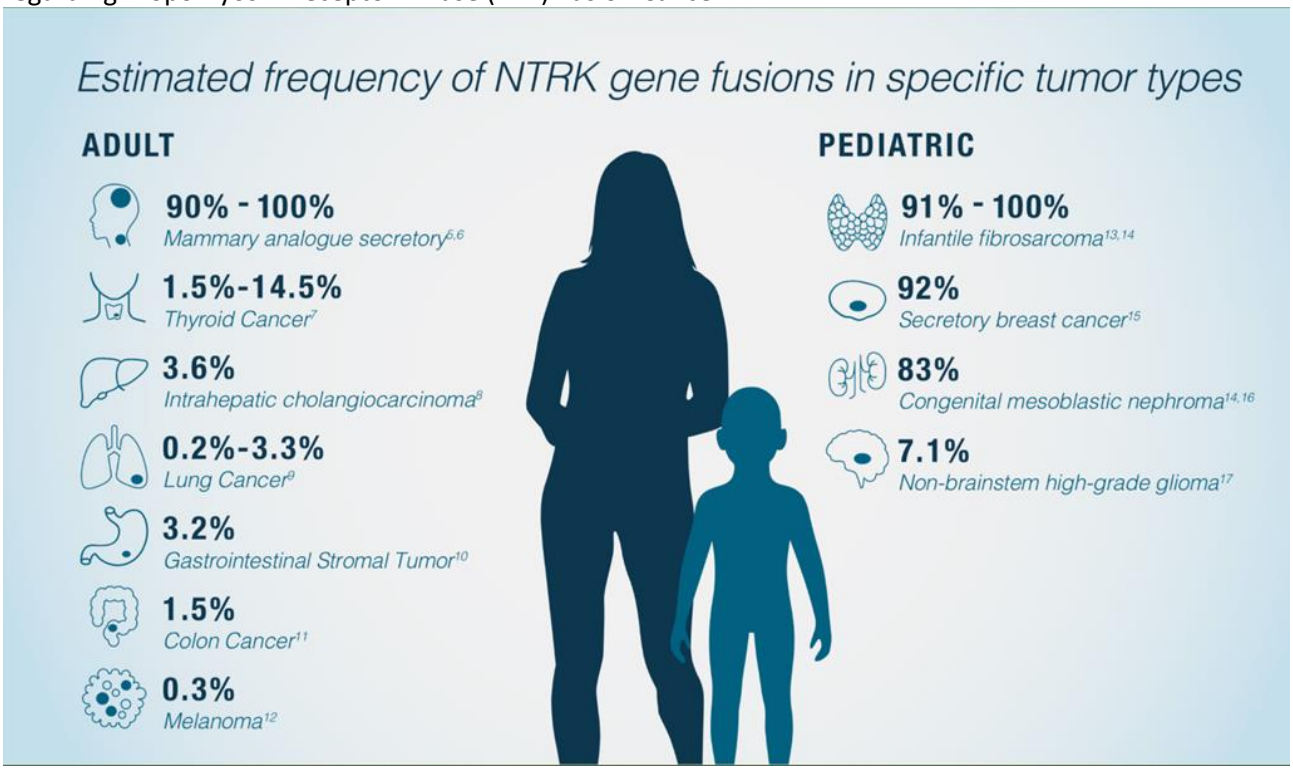
Incidence of Tropomyosin Receptor Kinase (TRK) Fusion Cancer

The outdated National Cancer Registry (2017), known for under reporting, does not provide any information regarding Tropomyosin Receptor Kinase (TRK) Fusion Cancer.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.

Wong, D., Yip, S. & Sorensen, P.H. 2020.

"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."

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.

Laetsch, T.W. & Hong, D.S. 2021.

"Chromosomal rearrangements of *NTRK1-3* resulting in gene fusions (*NTRK* gene fusions) have been clinically validated as oncogenic drivers in a wide range of human cancers. Typically, *NTRK* gene fusions involve both inter- and intrachromosomal fusions of the 5' regions of a variety of genes with the 3' regions of *NTRK* genes leading to TRK fusion proteins with constitutive, ligand-independent activation of the intrinsic tyrosine kinase. The incidence of *NTRK* gene fusions can range from the majority of cases in certain rare cancers to lower rates in a wide range of more common cancers. Two small-molecule TRK inhibitors have recently received regulatory approval for the treatment of patients with solid tumors harboring *NTRK* gene fusions, including the selective TRK inhibitor larotrectinib and the TRK/ROS1/ALK multikinase inhibitor entrectinib. In this review, we consider the practicalities of detecting tumors harboring *NTRK* gene fusions, the pharmacologic properties of TRK inhibitors currently in clinical development, the clinical evidence for larotrectinib and entrectinib efficacy, and possible resistance mechanisms."

Demetri, G.D., Antonescu, C.R., Bjerkehagen, B., Bovée, J.V.M.G., Boye, K., Chacón, M., Dei Tos, A.P., Desai, J., Fletcher, J.A., Gelderblom, H., George, S., Gronchi, A., Haas, R.L., Hindi, N., Hohenberger, P., Joensuu, H., Jones, R.L., Judson, I., Kang, Y.K., Kawai, A., Lazar, A.J., Le Cesne, A., Maestro, R., Maki, R.G., Martín, J., Patel, S., Penault-Llorca, F., Premanand Raut, C., Rutkowski, P., Safwat, A., Sbaraglia, M., Schaefer, I.M., Shen, L., Serrano, C., Schöffski, P., Stacchiotti, S., Sundby Hall, K., Tap, W.D., Thomas, D.M., Trent, J., Valverde, C., van der Graaf, W.T.A., von Mehren, M., Wagner, A., Wardelmann, E., Naito, Y., Zalcberg, J. & Blay, J.Y. 2020.

"Sarcomas are a heterogeneous group of malignancies with mesenchymal lineage differentiation. The discovery of neurotrophic tyrosine receptor kinase (NTRK) gene fusions as tissue-agnostic oncogenic drivers has led to new personalized therapies for a subset of patients with sarcoma in the form of tropomyosin receptor kinase (TRK) inhibitors. NTRK gene rearrangements and fusion transcripts can be detected with different molecular pathology techniques, while TRK protein expression can be demonstrated with immunohistochemistry. The rarity and diagnostic complexity of NTRK gene fusions raise a number of questions and challenges for clinicians. To address these challenges, the World Sarcoma Network convened two meetings of expert adult oncologists and pathologists and subsequently developed this article to provide practical guidance on the management of patients with sarcoma harboring NTRK gene fusions. We propose a diagnostic strategy that considers disease stage and histologic and molecular subtypes to facilitate routine testing for TRK expression and subsequent testing for NTRK gene fusions."

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/

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

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