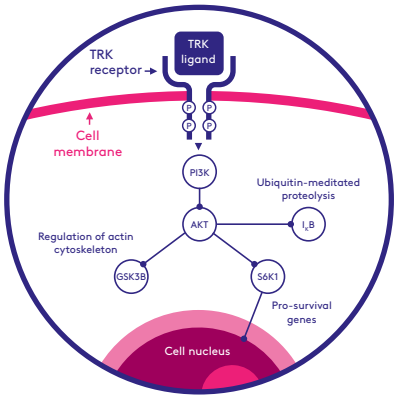
Better testing, better outcomes in Rare Cancer: **NTRK fusions**

NTRK inhibitor background

Genetic alterations in NTRK genes result in TRK fusions which directly induce cancer cell proliferation in multiple tumor types including both adults and children. The diverse nature of TRK fusions present challenges for identification and diagnosis given their rarity and heterogenous patient populations. Given the successful approval of pan TRK inhibitors, identification of patients with TRK-fusions, would be beneficial to enhance patient outcomes.

The first selective small-molecule kinase inhibitor, started its development specifically in patients with tumors dependent on signals from NTRK-fusion events across multiple tumor types. It blocks the ATP-binding site of the TRK family of receptors (TRKA, TRKB, and TRKC) in both pediatric and adult populations, in a tissue-agnostic fashion.



Development timeline

1982 — NTRK1 identified as an oncogene in colon cancer biopsy

1987 — First fusion identified in infantile fibrosarcoma (ETV6-NTRK3)

2010 — NTRK2 fusion identified in pilocytic astrocytoma, the most common childhood brain tumor

2013 — NTRK fusions identified in small frequency in lung adenocarcinoma

2014 — Clinical response in first patient with TRKA fusion using a TRK inhibitor – Larotrectinib enters phase I clinical trial for NTRK fusion in advanced solid tumors

2015 — Entrectinib granted FDA orphan designation for NTRK fusion positive NSCLC, CRC and neuroblastoma

2016 — First pediatric patient with infantile fibrosarcoma treated with Larotrectinib; Breakthrough Therapy Designation from the FDA received in July

2017 — Larotrectinib reported efficacy in 56 NTRK fusion positive patients (adults and pediatrics)

2018 — Larotrectinib granted breakthrough designation by FDA (first initial tumor-agnostic approval, second overall tumor-agnostic approval)

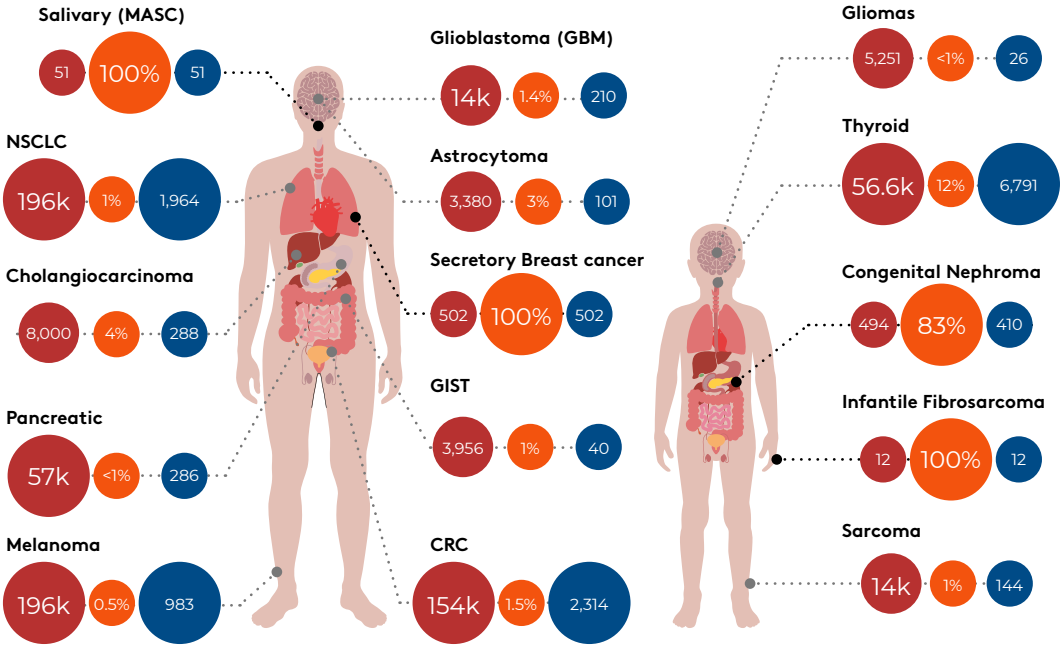
2019 — 2nd generation TRK inhibitors enter clinical trials

Entrectinib is the second drug approved by FDA for the treatment of cancers with NTRK fusions.

Epidemiology estimates in the United States

- Incident patients
- NTRK%
- NTRK patients
- Common cancer with low NTRK fusion frequency
- Rare cancer with high NTRK fusion frequency

The estimated frequency of NTRK-fusions across all tumors is less than 2% of cancer patients; however, for certain rare pediatric and adult cancers NTRK gene fusions are essentially pathognomonic, occurring >90%. Determining the true occurrence of NTRK gene fusions across a wide spectrum of tumor types is challenging lacking widespread testing. These values may have biases, but as testing for NTRK gene fusions is increasingly adopted, a better estimate of true incidence across a wide spectrum of cancer patients will likely emerge.



Findings

The routine identification of tumors harboring NTRK gene fusions is clinically important given availability of effective treatment.

NTRK fusions are rare occurring in <2% of cancer patients in the US and the clinical identification of them presents challenges

NTRK testing rates are variable across tumor types ranging from 36%-58% prior to 1st line

Lacking widespread testing the estimated number of patients could change, but given the heterogeneity across tumors one single diagnostic approach is likely not feasible

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Huang et al. Cell 177, March 21, 2019 © 2019 Elsevier Inc
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