Optimizing Precision Medicine in Cancer: Tumor Agnostic Treatment of TRK FUSION-POSITIVE CANCERS
Optimizing Precision Medicine in Cancer: Tumor Agnostic Treatment of TRK Fusion-Positive Cancers

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PROGRAM OVERVIEW
The case-based live activity will cover the treatment and management of patients with TRK fusion-positive cancer.

TARGET AUDIENCE
This activity is designed to educate community medical oncologists, pediatric medical oncologists, pathologists, oncology nurses and other healthcare providers involved in the care of patients with advanced TRK fusion-positive cancers in adults and children.

LEARNING OBJECTIVES
After completing the CME activity, learners should be better able to:

- Describe the pathogenesis driven by TRK pathway mutations across multiple tumor types
- Discuss the clinical trial data for both children and adults who have TRK fusion positive solid tumors treated with TRK inhibition
- Review current treatment and testing guidelines for TRK fusion driven tumors for both children and adults
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NURSING CREDIT INFORMATION
Purpose: This program would be beneficial for nurses involved in the care of patients with advanced TRK fusion-positive cancers in adults and children. Credits: 1.0 ANCC Contact Hour.

ACCREDITATION STATEMENT
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Dr. Hong receives consulting fees from Alpha Insights, Acuta, Amgen, Axiom, Adaptimmune, Baxter, Bayer, Genentech, GLG, Group H, Guidepoint, Infinity, Janssen, Merrimack, Medscape, Numab, Pfizer,
Prime Oncology, Seattle Genetics, Takeda, Trieza Therapeutics, and WebMD; he has been contracted for research with AbbVie, Adaptimmune, Aldi-Norte, Amgen, Astra-Zeneca, Bayer, BMS, Daiichi-Sankyo, Eisai, Fate Therapeutics, Genentech, Genmab, Ignyta, Infinity, Kite, Kyowa, Lilly, LOXO, Merck, MedImmune, Mirati, miRNA, Molecular Templates, Mologen, NCI-CTEP, Novartis, Pfizer, Seattle Genetics, Takeda, and Turning Point Therapeutics. He has ownership interest in Molecular Match (Advisor), OncoResponse (Founder), and Presagia Inc. (Advisor). Dr. Hong has also reported the following other disclosures: Travel, Accommodations, Expenses: Bayer, LOXO, miRNA, Genmab, AACR, ASCO, and SITC.

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2. Participate in the live activity.
3. Complete the online post-test and evaluation.
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Program Agenda

I. Pathogenesis of TRK Fusions, Independent of Tumor Type

   a. What is a TRK fusion mutation?
      i. Advances in biology and therapeutic targeting of TRK signaling
      ii. Genomic aberrations involving NTRK
   b. NTRK fusion gene structures and tumor types
      i. Variety of solid tumors are driven by fusion mutations
   c. Detection
      i. Testing for TRK fusions (RNA sequencing, FISH, Pan-TRK IHC, etc)

II. NCCN Guideline Evidence-Based Recommendations to Optimize Treatment for TRK Fusion Driven Cancers

   a. Targeted therapy: activity of first-generation TRK inhibitors
      i. TRK inhibitors – background and mechanisms
         • Larotrectinib – clinical trials data review
         • Entrectinib – clinical trials data review
      ii. On-target side effects
   b. Resistance and sequential TKI therapy
   c. Future/investigational agents
      • Repotrectinib
      • Selitrectinib

III. Integrated Approach to Treating TRK Fusion-Positive Cancers

   a. Multidisciplinary care
   b. Case Studies

IV. Conclusions

V. Questions & Answers
Optimizing Precision Medicine in Cancer: Tumor-Agnostic Treatment of TRK Fusion-Positive Cancers

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Disclosures

• Please see Program Overview for specific speaker disclosure information.

• During the course of this lecture, the faculty may mention the use of medications for both FDA-approved and non-approved indications.

This activity is supported by an educational grant from Bayer HealthCare Pharmaceuticals, Inc.
Agenda

• Describe TRK fusion oncogenesis

• Identify tumors that harbor TRK fusions

• Discuss clinical trials for both children and adults with TRK fusion-positive solid tumors treated with TRK inhibition

• Review current treatment and testing guidelines for TRK fusion-driven tumors for children and adults

Pathogenesis
**Key Advances in Biology and Therapeutic Targeting of TRK Signaling**

- **1950s**: Identification of nerve growth factor (NGF), the first neurotrophin
- **1985**: Identification of nerve growth factor (NGF), the first neurotrophin
- **1989–1991**: Identification of TRKA, TRKB, and TRKC as high-affinity neurotrophin receptors
- **1993–1994**: Crystal structure of NGF in complex with TRKA determined
- **2000**: Identification of neurotrophin 3 (NT3) and neurotrophin 4 (NT4)
- **2010**: Identification of the first NTRK2 fusion (ETV6-NTRK2) in infantile fibrosarcoma
- **2015**: First activating TRK alternative variant identified
- **2017**: TRK downregulation associated with hyperphagia and hyperdipsia in mice
- **2018**: Larotrectinib achieves histology-agnostic and age-agnostic responses in NTRK fusion-positive solid tumors
- **2018**: Second-generation TRK inhibitors enter clinical trial testing

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**TRK Signaling**

- Ligand specificity of TRK proteins for neurotrophins that bind to their cognate receptors as a homodimer.
- NTRK fusions result in ligand-independent signaling and activate downstream pathways that result in oncogenesis.

**NT-3/4 = neurotrophin 3/4; NGF = nerve growth factor; BDNF = brain-derived neurotrophic factor.**

**NTRK Fusion Gene Structure**

- **Known dimerization domain**
  - NH₂ → Coiled coil domain
  - Zinc finger domain
  - WD domain

- **Alternate dimerization mechanism**
  - NH₂ → Transmembrane domain

- **Unknown mechanism**
  - NH₂ → Transmembrane domain

**NTRK fusion**
- 5’ upstream gene partner
- 3’ 1’ NTRK1  NTRK2  NTRK3

**Transmembrane domain**
- COOH
- Tyrosine kinase domain

**WD** = tryptophan-aspartic acid.


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**Frequency of NTRK Fusions in Adult and Pediatric Tumors**

- **Cancers enriched for TRK fusions**
  - Frequency >90%
- **Cancers harboring TRK fusions at lower frequencies**
  - 5–25%
  - <5%

**GI** = gastrointestinal.

Detection

Testing for TRK Fusions

• Unlike somatic mutation assessment, NTRK fusion detection is not as straightforward.

• Various assays exist that interrogate DNA, RNA, and protein
  – IHC
  – FISH
  – RNA/DNA sequencing
  – Pan-TRK immunohistochemistry

• Assay selection can depend on tumor type and genes involved, available material, and assay accessibility/payer coverage.

DNA = deoxyribonucleic acid; RNA = ribonucleic acid; IHC = immunohistochemistry; FISH = fluorescence in situ hybridization.
Features of Techniques to Detect NTRK Rearrangements

<table>
<thead>
<tr>
<th>Method</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Detection of</th>
<th>Screening</th>
</tr>
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<tbody>
<tr>
<td>IHC</td>
<td>High*</td>
<td>High†</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>FISH#</td>
<td>High</td>
<td>High</td>
<td>One per probe</td>
<td>No</td>
</tr>
<tr>
<td>RNA seq NGS</td>
<td>High</td>
<td>High</td>
<td>Yes</td>
<td>Yes—RNA</td>
</tr>
<tr>
<td>DNA seq#</td>
<td>Moderate</td>
<td>High</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

When payer coverage is not an issue, the best method to maximize NTRK fusion identification is NGS, preferably with both a DNA and RNA component.

\*False negatives reported mainly in NTRK3 fusions; \†in the absence of smooth muscle/neuronal differentiation; \#Detected rearrangements by DNA-based assays may not result in fusions, and correlation with surgical pathology and predicted transcript (for sequencing) is needed.

NGS = next-generation sequencing.

RNA Sequencing Can Help Identify Fusions Not Detected by DNA Sequencing

Clinical benefit of matched targeted therapy

<table>
<thead>
<tr>
<th>Rearrangement</th>
<th>Matched therapy</th>
<th>Best response</th>
</tr>
</thead>
<tbody>
<tr>
<td>EML4-ALK</td>
<td>Alecetinib Entrectinib</td>
<td>SD</td>
</tr>
<tr>
<td>CD74-ROS1</td>
<td>Larotrectinib</td>
<td>PR</td>
</tr>
<tr>
<td>SQSTM1-NTRK3</td>
<td>Entrectinib</td>
<td>SD</td>
</tr>
<tr>
<td>STRN-NTRK2</td>
<td>MET Exon14 skipping SLC34A2-ROS1 SLC34A2-ROS1 SDC4-NRG1</td>
<td>PD</td>
</tr>
<tr>
<td>CD74-NRG1</td>
<td>Afatinib</td>
<td>SD</td>
</tr>
<tr>
<td>CD74-ROS1</td>
<td>Crizotinib</td>
<td>SD</td>
</tr>
<tr>
<td>MET Exon14</td>
<td>Crizotinib</td>
<td>SD</td>
</tr>
<tr>
<td>MET Exon14</td>
<td>Crizotinib</td>
<td>PD</td>
</tr>
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SD = stable disease; PR = partial response; PD = progressive disease.
Pan-Trk IHC Has High Sensitivity and Specificity as Screening Tool for NTRK Fusions

- Pan-Trk IHC (mAb EPR17341)
  - Positive in 20/21 cases with NTRK fusion confirmed by Archer (RNA sequencing)
  - All 20 additional Archer-negative cases had concordant pan-TRK IHC results
- Sensitivity = 95.2%; specificity = 100% for transcribed NTRK fusions

ESMO Strategy for Detecting NTRK1/2/3 Fusion Genes

Sample to be investigated for the presence of NTRK fusions

- As a confirmatory technique, use FISH, RT-PCR, or targeted RNA NGS assays with specific probes for the fusion involving the known NTRK gene.

Is the histologic tumor type known to harbor highly recurrent NTRK Fusions?

- YES
- NO

Is there a sequencing platform available?

- YES
- NO

Use IHC as a screening tool

- NO TRK expression
- Detection of TRK expression

IHC to confirm protein expression in positive cases

Use front-line NGS reliably detecting NTRK fusions, preferably including RNA testing when possible

mAb = monoclonal antibody.


RT-PCR = reverse transcription-polymerase chain reaction.
Targeted Therapy: Activity of 1st-Generation TRK Inhibitors

TRK Inhibition: Background

1st-generation TRK inhibitors were granted landmark, tumor-agnostic approvals in 2018 (larotrectinib) and 2019 (entrectinib).

<table>
<thead>
<tr>
<th>TRK Inhibitors</th>
<th>Larotrectinib</th>
<th>Entrectinib</th>
<th>Selitrectinib*</th>
<th>Repotrectinib*</th>
</tr>
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<tbody>
<tr>
<td><strong>Generation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>First</td>
<td>✔️</td>
<td>✔️</td>
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<tr>
<td>Second</td>
<td></td>
<td></td>
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<tr>
<td><strong>Inhibits</strong></td>
<td></td>
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</tr>
<tr>
<td>TRKA/B/C</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>ROS1</td>
<td></td>
<td></td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>ALK</td>
<td></td>
<td></td>
<td></td>
<td>✔️</td>
</tr>
<tr>
<td><strong>Resistance</strong></td>
<td></td>
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<td></td>
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<tr>
<td>Inhibits most NTRK</td>
<td></td>
<td></td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>resistance mutations</td>
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</tbody>
</table>

Not FDA approved.
Larotrectinib—Selective TRK Inhibitor
Antitumor Activity in TRK Fusion-Positive Cancers

Methods

• First study released
  – 55 patients, aged 4 months to 76 years, with TRK fusion-positive cancers

• 3 protocols
  – Phase 1 study of adults
  – Phase 1–2 study of children
  – Phase 2 study of adolescents and adults

• Primary endpoint = overall response rate

• Secondary endpoints = DoR, PFS, safety

DoR = duration of response; PFS = progression-free survival


Larotrectinib in Pediatric and Adult Patients
Marked and Durable Antitumor Activity

Maximum change in tumor size, according to tumor type

Maximum change in tumor size [%]

*TRK resistance mutation due to previous therapy; †pathological complete response.
GIST = gastrointestinal stromal tumor; IFS = infantile fibrosarcoma.

Larotrectinib
Secondary Outcomes

DoR in responders

PFS among all patients


Update of Prior Data Set in 102 patients

NCT02122913 (adults, phase 1)
12 patients contributed to efficacy analysis
• 8 in primary analysis set
• 4 in supplemental analysis set

NCT02637687 (children, phase 1/2)
50 patients contributed to efficacy analysis
• 12 in primary analysis set
• 38 in supplemental analysis set

NCT02576431 (adults and children, phase 2)
97 patients contributed to efficacy analysis
• 35 in primary analysis set
• 62 in supplemental analysis set

159 treated patients with TRK fusion-positive tumors in efficacy analysis set
• 55 in primary analysis set
• 104 in supplemental analysis set

57 discontinued treatment
• 36 disease progression
• 5 patient decision
• 2 adverse events
• 2 physician decision
• 2 protocol deviation
• 2 died
• 8 other reasons

102 remained on treatment

Larotrectinib in Pediatric and Adult Patients
Updated Outcomes in Larger Data Set

- Median duration of response = 35.2 months
- 80% responses ongoing at 12 months
- Median PFS = 28.3 months

*Maximum change in tumor size of 93% growth; †Brain metastases; ‡Pathological complete response.


Entrectinib—Multikinase TRK Inhibitor

- 3 phase 1/2 clinical trials: ALKA-372-001, STARTRK-1, and STARTRK-2
- 54 pts ≥18 years (adults) with metastatic or locally advanced NTRK fusion-positive solid tumors who received entrectinib ≥600 mg/d

<table>
<thead>
<tr>
<th>Activity Outcomes</th>
<th>Efficacy-evaluable population (n = 54)</th>
<th>Patients with baseline CNS disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients achieving a response, n (%)</td>
<td>Yes (n = 12)</td>
</tr>
<tr>
<td>Best overall response, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>4 (7%)</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>27 (50%)</td>
<td>6 (50%)</td>
</tr>
<tr>
<td>SD</td>
<td>9 (17%)</td>
<td>4 (33%)</td>
</tr>
<tr>
<td>PD</td>
<td>4 (7%)</td>
<td>0</td>
</tr>
<tr>
<td>Non-CR or PD</td>
<td>0</td>
<td>4 (10%)</td>
</tr>
<tr>
<td>Missing or unevaluable</td>
<td>3 (6%)</td>
<td>2 (17%)</td>
</tr>
<tr>
<td>Median DoR, mo (95% CI)</td>
<td>10.4 (7.1–NE)</td>
<td>NE</td>
</tr>
<tr>
<td>Median PFS, mo (95% CI)</td>
<td>11.2 (8.0–14.9)</td>
<td>7.7 (4.7–NE)</td>
</tr>
</tbody>
</table>

CNS = central nervous system; CR = complete response; mo = month(s); NE = not estimable.

Entrectinib in Adult Patients
Marked and Durable Antitumor Activity

Median duration of response = 10 months

SLD = sum of largest diameter; MASC = mammary analogue secretory carcinoma; NSCLC = non-small-cell lung cancer.

Entrectinib in Adult Patients
Secondary Outcomes

PFS (median = 11 months)

OS (median = 21 months)

OS = overall survival.
Targeted Therapy: On-Target Side-Effects

Loss, Decreased Activity, or Inhibition of TRK

**Neurological consequences**
- Development of obesity caused by hyperphagia and hyperdipsia in mice (NTRK2 mutant)
- Defect in proprioception, impairment of motor neuron afferents, and loss of a population of dorsal root ganglia neurons (NTRK3 null)
- Lack populations of motor neurons as well as dorsal root and trigeminal neurons (NTRK3 null)
- Severe sensory and sympathetic neuropathies (NTRK1 null)
- Congenital insensitivity to pain with anhidrosis (CIPA) (NTRK1 mutant)

**Non-neurological consequences**
- Increased apoptosis of cardiac endothelial cells and decrease in intramyocardial blood vessel density (NTRK2 null)
- Atrial end ventricular septal defects and valvular defects (NTRK3 null)
- Inhibition of ovulation in mice (TRKA inhibition)

Select Adverse Events: Entrectinib/Larotrectinib*

*To benchmark frequency of AEs, crizotinib, which has well-known safety profile, was chosen for comparison. AE = adverse event; ALT = alanine aminotransferase.

Resistance and Sequential TKI Therapy
First-Generation TRK Inhibitor Resistance Can Be Mediated By On-Target Mechanisms

<table>
<thead>
<tr>
<th>TRKA</th>
<th>TRKB</th>
<th>TRKC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solvent front (SF)</td>
<td>xDFG</td>
<td>Gatekeeper (GK)</td>
</tr>
</tbody>
</table>

TRKA: G061S, F589L, G667C, G667S, G696A
TRKB: G623R, G696A

WT = wild type; xDFG = X-aspartate-phenylalanine-glycine.

Repotrectinib*—Next Generation Multikinase TRK Inhibitor

- Use of TKI with activity against ROS1/TRK/ALK can result in significant benefit in tumors harboring ALK, ROS1, or NTRK1–3 rearrangements, but resistance invariably develops
- The emergence of on-target kinase domain mutations is a major mechanism of acquired resistance
- Repotrectinib (TPX-0005)
  - A rationally designed, LMW, macrocyclic TKI
  - Selective and highly potent against ROS1, TRKA–C, and ALK
  - Exhibits activity against several solvent-front substitutions *in vitro* and *in vivo*

TKI = tyrosine kinase inhibitor; LMW = low molecular weight.

*Not approved by the FDA
Repotrectinib*: Efficacy in NIH303 LMNA TRKA WT and G595R Tumors ROS1/TRK/ALK Inhibitor

Antitumor activity of repotrectinib in NIH3T3 LMNA-TRKA WT tumors

Antitumor activity of repotrectinib in NIH3T3 LMNA-TRKAG595R tumors

BID = twice daily; TGI = tumor growth inhibition.


*Not approved by the FDA

ETV6-NTRK3-Rearranged MASC With NYRK3G623E-Mediated Resistance to Entrectinib

Selitrectinib (LOXO-195)* Overcomes Acquired Resistance to Prior TRK Kinase Inhibition

TRK-expressing NIH 3T3 cells were treated with selitrectinib or larotrectinib for 1 hour, followed by ELISA or flow cytometry to assess phospho-TRK levels.

ELISA = enzyme-linked immunosorbent assay; ∆ = change in.


*Not approved by the FDA

Selitrectinib* Is Active In TRK Fusion-Positive Cancers With Various Resistance Mutations

7 patients were non-evaluable; 1 single-patient-protocol patient with SF kinase mutation had PD and is not included.

*Patients with responses at or close to 0%; †SPP population.


*Not approved by the FDA
Integrated Approach to Treating TRK Fusion-Positive Cancers

Multidisciplinary Care

A multi-disciplinary team with experience and expertise is needed to effectively manage these patients.

- Adult/pediatric medical oncologist
- Surgical/radiation oncologist
- Pathologist
- Molecular diagnostics
**Sequential Therapy**

For oligo/solitary site progression, consider local therapy and continued TKI use.

Potential mechanisms identified:
- KRAS mutation
- MET amplification
- BRAF mutation
- IGF1R activation

**Resistance**

<table>
<thead>
<tr>
<th>Solvent front</th>
<th>Gatekeeper</th>
<th>xDFG</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>G595R</td>
<td>F589L</td>
<td>G667C</td>
<td>A608D</td>
</tr>
<tr>
<td>G639R</td>
<td>F633L</td>
<td>G709C</td>
<td></td>
</tr>
<tr>
<td>G623R</td>
<td>F617L</td>
<td>G696A</td>
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</table>

**On-target resistance**

**Off-target resistance**

Repotrectinib
Selitrectinib

2nd generation
TRK Inhibitor

1st-generation
TRK Inhibitor

Entrectinib
Larotrectinib


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**Case One: Presentation**

- A 1-year-old boy presents with a bulky right-knee tumor. Biopsy shows congenital fibrosarcoma. No metastases are identified on an initial workup.

- Which of the following statements is **true**?
  a) There is a <1% chance that a TRK fusion will be found.
  b) TRK fusions are not found in pediatric cancers.
  c) Amputation is the preferred treatment option.
  d) This histology is enriched for TRK fusions.
Case One: Presentation

• A 1-year-old boy presents with a bulky right knee tumor. Biopsy shows congenital fibrosarcoma. No metastases are identified on an initial workup.

• Which of the following statements is true?
  a) There is a <1% chance that a TRK fusion will be found.
  b) TRK fusions are not found in pediatric cancers.
  c) Amputation is the preferred treatment option.
  d) This histology is enriched for TRK fusions.

Case One: Molecular Testing

• Molecular testing is recommended to determine if a TRK fusion is present.

• Which of the following statements is false?
  a) Pan-TRK IHC can detect the specific TRK fusion type in this cancer.
  b) NGS is a reasonable up-front strategy to identify a TRK fusion.
  c) If DNA-based NGS is negative, RNA-based NGS testing should be considered.
  d) Three sets of break-apart FISH probes are required to interrogate *NTRK1/2/3*. 
Case One: Molecular Testing

• Molecular testing is recommended to determine if a TRK fusion is present.

• Which of the following statements is false?
  a) Pan-TRK IHC can detect the specific TRK fusion type in this cancer.
  b) NGS is a reasonable up-front strategy to identify a TRK fusion.
  c) If DNA-based NGS is negative, RNA-based NGS testing should be considered.
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Case One: Fusion Identified

• An ETV6-NTRK3 fusion is identified by RNA-based NGS, and orthogonal pan-TRK IHC testing is positive for TRK expression.

• Which of the following statements is true?
  a) Entrectinib is unlikely to be active against this cancer.
  b) Larotrectinib is approved for the treatment of this non-metastatic, TRK fusion-positive cancer.
  c) Response to TRK inhibition is more pronounced in NTRK1 fusions compared with NTRK3 fusions.
  d) Adults with TRK fusion-positive cancers are more likely to benefit from TRK inhibition.

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Case Two: Presentation

- A 42-year-old female with widely metastatic melanoma is found to harbor an \textit{NTRK1} fusion in her cancer. She is treated with entrectinib with a durable 3-year response, followed by a subsequent progression.

- Which of the following statements is \textbf{true}?
  a) Next-generation TRK TKIs are not yet available in the clinic.
  b) Immunotherapy is the only systemic therapy option for this patient.
  c) Sequencing of a progressive lesion showing an acquired \textit{NTRK1} mutation is suggestive of on-target resistance.
  d) Surgery or radiation for a pattern of solitary site progression is unlikely to yield benefit.

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Case Two: NTRKI G595R Mutation

- An NTRKI G595R mutation is identified along with the original fusion.

- Which of the following approaches does not represent a reasonable treatment option for this patient?
  a) Selitrectinib
  b) Larotrectinib
  c) Standard-of-care chemotherapy
  d) Repotrectinib

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  b) Larotrectinib
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Case Two: Treatment

• Repotrectinib is initiated on trial. The patient responds to therapy; however, a year later, her weight starts to progressively increase. A physical exam is unremarkable for fluid retention. No intervention has yet been tried.

• Which of the following statements is true?
  a) Weight gain is an on-target consequence of TRK TKI therapy.
  b) Dose modification should not be considered in patients with refractory TRK inhibitor-related weight gain.
  c) Accompanying dizziness or paresthesia does not represent concurrent on-target adverse events.
  d) The TKI should be permanently discontinued at this point.

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**Conclusions**

- **NTRK** fusions, encoding TRK-fusion proteins, are oncogenic drivers of adult and pediatric tumors, which has supported a basket-trial approach to drug development

- These fusions are found at high frequencies in rare cancer types and lower frequencies in other tumor types

- TRK fusions are clinically actionable, ie, 1st-generation TRK inhibitors (larotrectinib or entrectinib) result in histology- and age-agnostic activity

- Resistance to TRK inhibition can be mediated by the acquisition of NTRK kinase domain mutations for which 2nd-generation TRK inhibitors (selitrectinib and repotrectinib) have been developed

- TRK inhibitors are well-tolerated; occasional on-target adverse effects are predictable

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Thank You!
# TRK Fusion-Positive Cancer: Identification, Diagnosis and Management

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### Resources and Societies

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