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

This activity is provided by Med Learning Group. *This activity is supported by an educational grant from Bayer HealthCare Pharmaceuticals, Inc.*
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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.

Dr. Laetsch receives consulting fees from Bayer, Novartis, and Cellectis; he is contracted for research with Bayer, Novartis, and Pfizer.

Dr. Ou receives consulting fees from AstraZeneca, Pfizer, Roche/Genentech, Takeda/ARIAD, Daiichi Sankyo, and JNJ; he serves on the speakers' bureau for AstraZeneca, Pfizer and Roche/Genentech, and Takeda; and has ownership interest in Turning Point Therapeutics Inc.

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The reviewer of this activity has nothing to disclose.

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2. Participate in the live activity.
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Co-provided by Ultimate Medical Academy/Complete Conference Management (CCM).

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

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

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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.

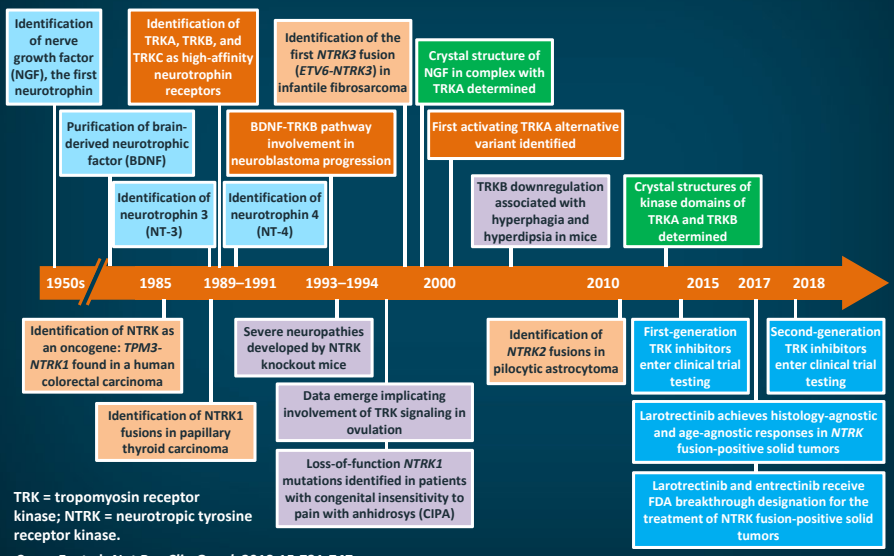
This activity is supported by an educational grant from Bayer HealthCare Pharmaceuticals, Inc.

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

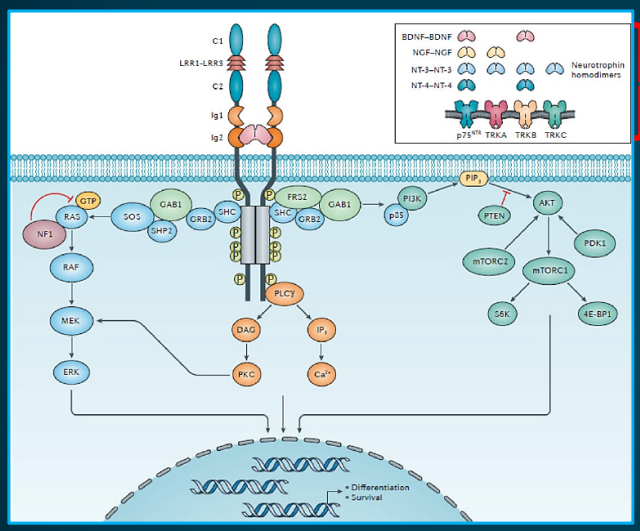
Key Advances in Biology and Therapeutic Targeting of TRK Signaling



TRK = tropomyosin receptor kinase; NTRK = neurotropic tyrosine receptor kinase.

Cocco E, et al. *Nat Rev Clin Oncol*. 2018;15:731-747.

TRK Signaling

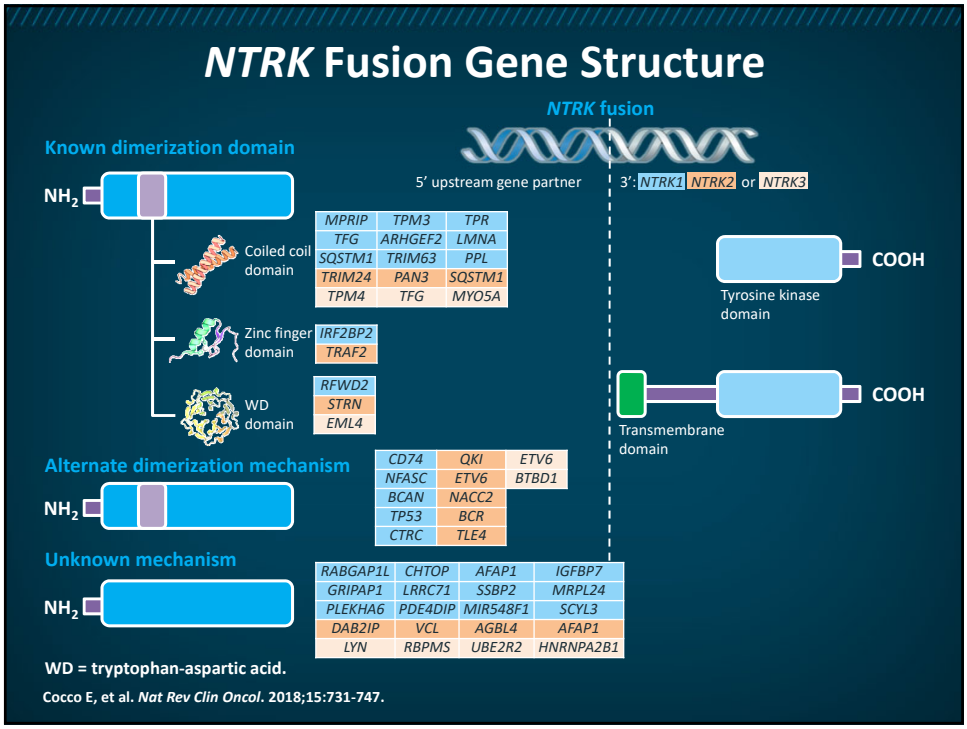


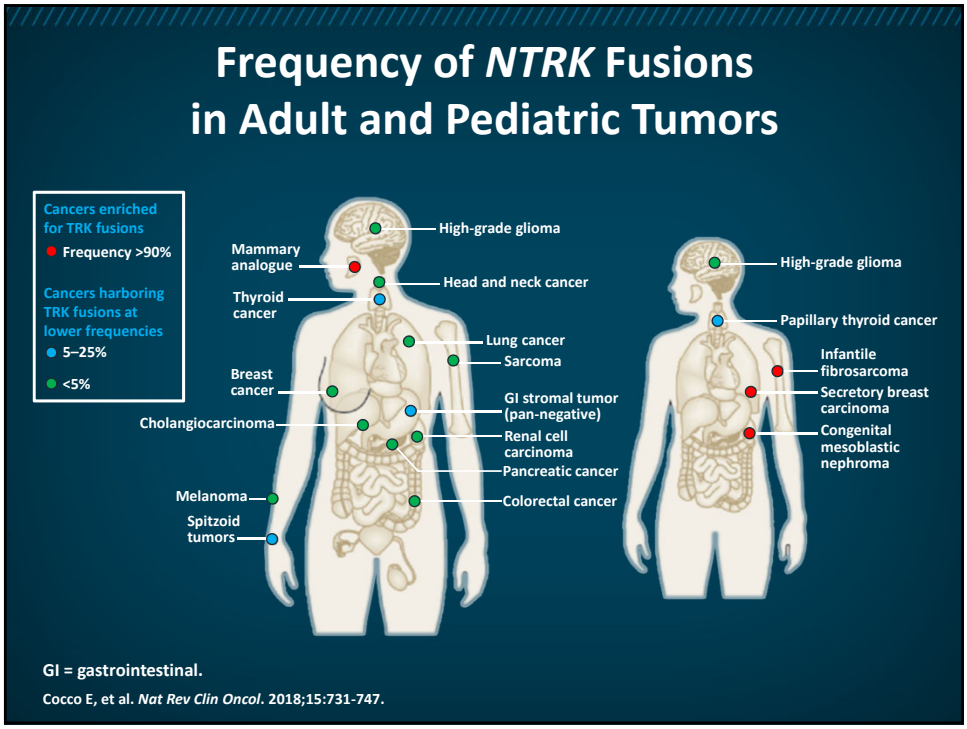
Ligand specificity of TRK proteins for neurotrophins that bind to their cognate receptors as a homodimer.

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.

Cocco E, et al. *Nat Rev Clin Oncol*. 2018;15:731-747.


NTRK Fusion Gene Structure
NTRK fusion
Known dimerization domain
NH2
5′ upstream gene partner
3′: NTRK1 NTRK2 or NTRK3
MPRIP TPM3 TPR
TFG ARHGEF2 LMNA
SQSTM1 TRIM63 PPL
TRIM24 PAN3 SQSTM1
TPM4 TFG MYO5A
Coiled coil domain
COOH
Tyrosine kinase domain
Zinc finger domain
IRF2BP2
TRAF2
RFWD2
STRN
EML4
WD domain
COOH
Transmembrane domain
Alternate dimerization mechanism
NH2
CD74 QKI ETV6
NFASC ETV6 BTBD1
BCAN NACC2
TP53 BCR
CTRC TLE4
Unknown mechanism
NH2
RABGAP1L CHTOP AFAP1 IGFBP7
GRIPAP1 LRRC71 SSBP2 MRPL24
PLEKHA6 PDE4DIP MIR548F1 SCYL3
DAB2IP VCL AGBL4 AFAP1
LYN RBPMS UBE2R2 HNRNPA2B1
WD = tryptophan-aspartic acid.
Cocco E, et al. Nat Rev Clin Oncol. 2018;15:731-747.


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%
Mammary analogue
High-grade glioma
Head and neck cancer
Thyroid cancer
Lung cancer
Sarcoma
Breast cancer
GI stromal tumor (pan-negative)
Cholangiocarcinoma
Renal cell carcinoma
Pancreatic cancer
Melanoma
Colorectal cancer
Spitzoid tumors
High-grade glioma
Papillary thyroid cancer
Infantile fibrosarcoma
Secretory breast carcinoma
Congenital mesoblastic nephroma
GI = gastrointestinal.
Cocco E, et al. Nat Rev Clin Oncol. 2018;15:731-747.

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.

Soloman JP, et al. *Mod Pathol*. 2020;33:38-46.

Features of Techniques to Detect NTRK Rearrangements

Method	Sensitivity	Specificity	Detection of			Screening
			Fusions	Partner	Expression	
IHC	High*	High†	Yes	No	Yes—protein	Yes
FISH‡	High	High	One per probe	No	No	No
RNA seq NGS	High	High	Yes	Yes	Yes—RNA	Yes
DNA seq‡	Moderate	High	Yes	Yes	No	Yes

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.

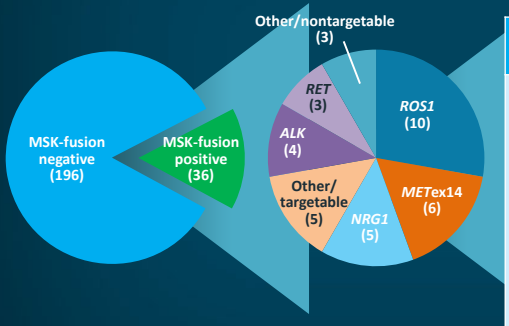
NGS = next-generation sequencing.

Marchiò C, et al. *Ann Oncol*. 2019;30:1417-1427.

RNA Sequencing Can Help Identify Fusions Not Detected by DNA Sequencing

MSK-IMPACT negative (n = 232)

MSK-fusion positive (n = 36)



Clinical benefit of matched targeted therapy (n = 10)

Rearrangement	Matched therapy	Best response
EML4-ALK	Alectinib	SD
CD74-ROS1	Entrectinib	SD
SQSTM1-NTRK3	Larotrectinib	PR
STRN-NTRK2	Larotrectinib	SD
CD74-ROS1	Entrectinib	PR
CD74-NRG1	Afatinib	SD
MET Exon14 skipping	Crizotinib	SD
SLC34A2-ROS1	Crizotinib	PD
SLC34A2-ROS1	Crizotinib	SD
SDC4-NRG1	Afatinib	PD

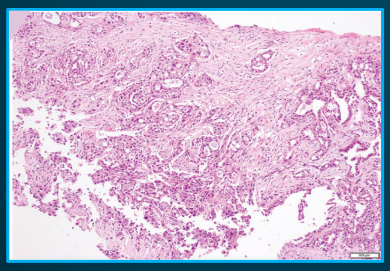
SD = stable disease; PR = partial response; PD = progressive disease.

Benayed R, et al. *Clin Cancer Res.* 2019;25:4712-4722.

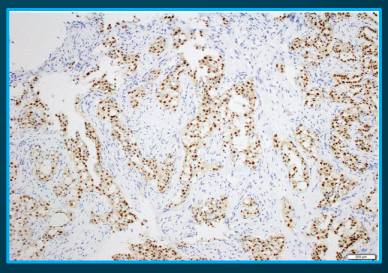
Pan-Trk IHC Has High Sensitivity and Specificity as Screening Tool for NTRK Fusions

- 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

Secretory breast carcinoma with vacuolated cytoplasm (H&E, 100x)



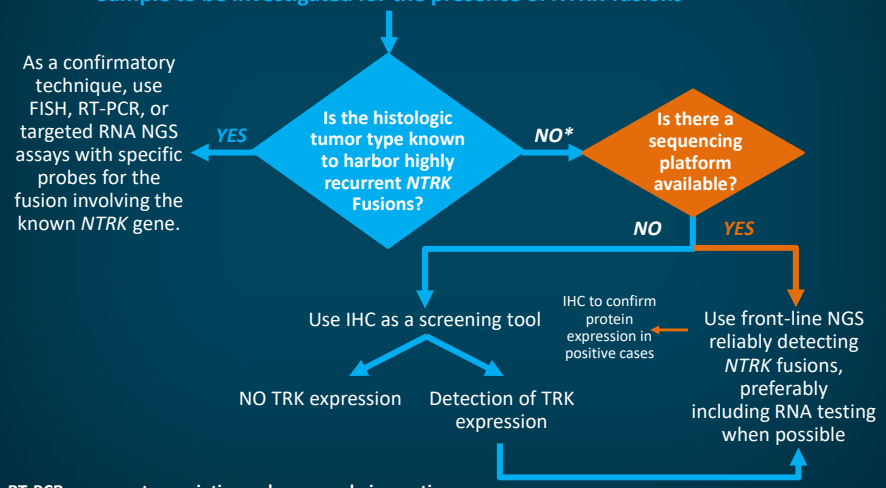
Strong nuclear and moderate staining for pan-TRK IHC (100x)



mAb = monoclonal antibody.

Hechtman JF, et al. *Am J Surg Pathol*. 2017;41;1547-1551.

ESMO Strategy for Detecting NTRK1/2/3 Fusion Genes



RT-PCR = reverse transcription-polymerase chain reaction.

Marchiò C, et al. *Ann Oncol*. 2019;30:1417-1427.

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).

TRK Inhibitors				
	Larotrectinib	Entrectinib	Selitrectinib*	Repotrectinib*
Generation				
First	✓	✓		
Second			✓	✓
Inhibits				
TRKA/B/C	✓	✓	✓	✓
ROS1		✓		✓
ALK		✓		✓
Resistance				
Inhibits most *NTRK* resistance mutations			✓	✓

Not FDA approved.

Drilon A. *Ann Oncol*. 2019;30(suppl 8):viii23-viii30.

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

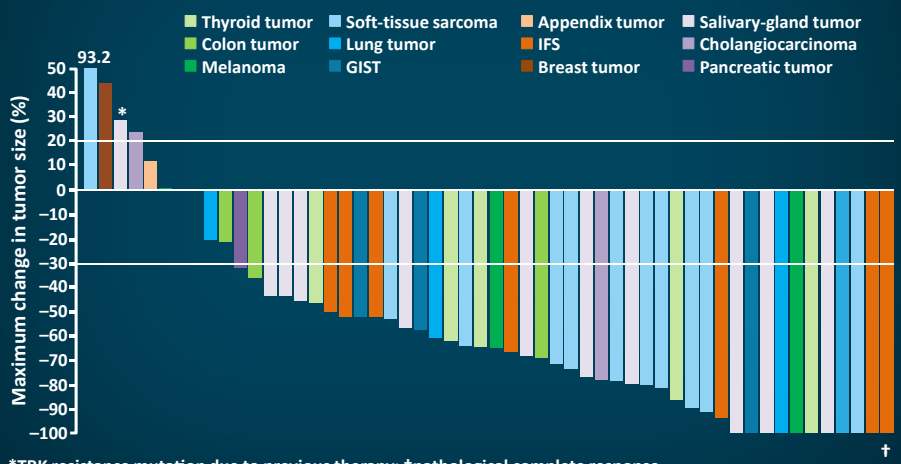
DoR = duration of response; PFS = progression-free survival

Drilon A, et al. *N Engl J Med*. 2018;378:731-739.

Larotrectinib in Pediatric and Adult Patients

Marked and Durable Antitumor Activity

Maximum change in tumor size, according to tumor type

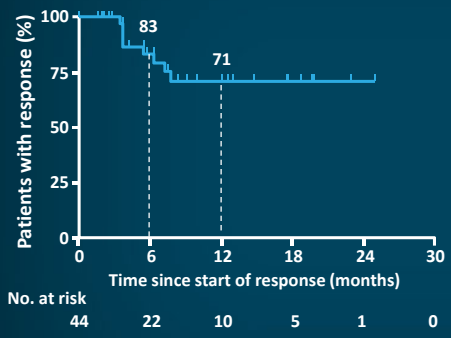


*TRK resistance mutation due to previous therapy; †pathological complete response.
GIST = gastrointestinal stromal tumor; IFS = infantile fibrosarcoma.

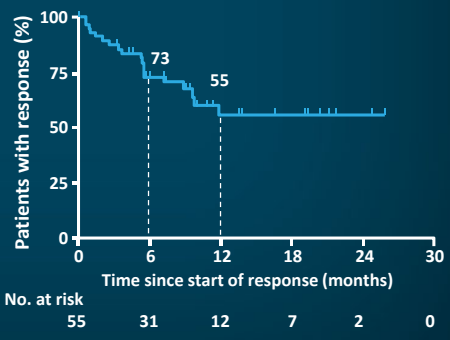
Drilon A, et al. *N Engl J Med*. 2018;378:731-739.

Larotrectinib
Secondary Outcomes

DoR in responders



PFS among all patients



Drilon A, et al. *N Engl J Med*. 2018;378:731-739.

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

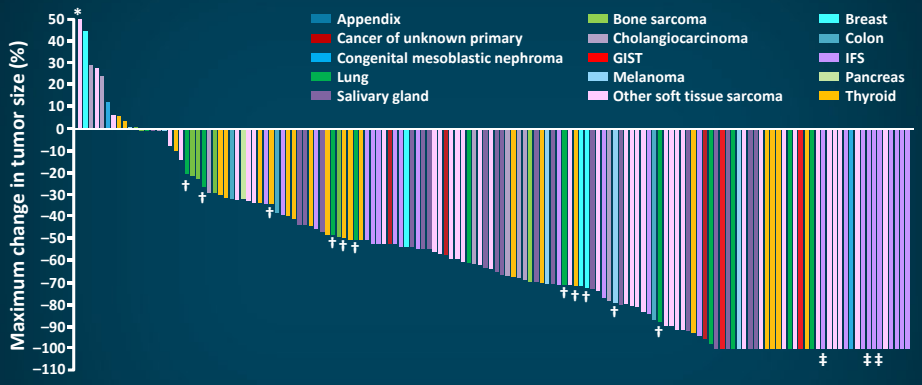
57 discontinued treatment
- 36 disease progression
- 5 patient decision
- 2 adverse events
- 2 physician decision
- 2 protocol deviation
- 2 died
- 8 other reasons

102 remained on treatment

Hong DS, et al. *Lancet Oncol*. 2020;21:531-540.

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.

Hong D, et al. *Lancet Oncology*. 2020;21:531-40. PMID 32105622.

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

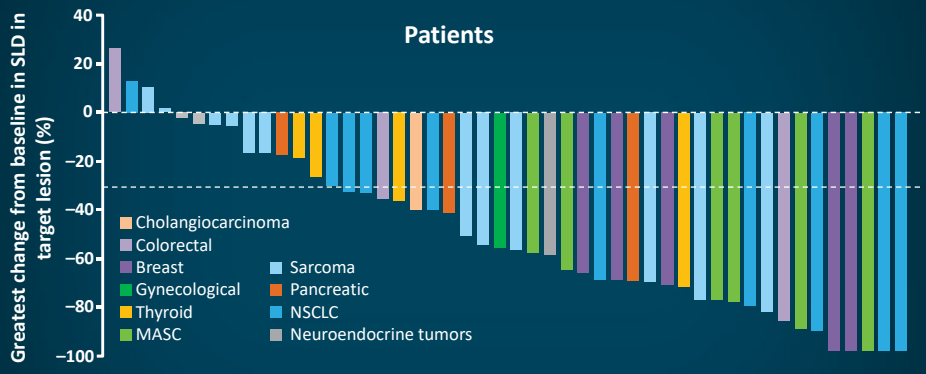
Activity Outcomes

	Efficacy-evaluable population (n = 54)	Patients with baseline CNS disease	
		Yes (n = 12)	No (n = 42)
Patients achieving a response, n (%)	31 (57%)	6 (50%)	25 (60%)
Best overall response, n (%)			
CR	4 (7%)	0	4 (10%)
PR	27 (50%)	6 (50%)	21 (50%)
SD	9 (17%)	4 (33%)	5 (12%)
PD	4 (7%)	0	4 (10%)
Non-CR or PD	3 (6%)	0	3 (7%)
Missing or unevaluable	7 (13%)	2 (17%)	5 (12%)
Median DoR, mo, (95% CI)	10.4 (7.1–NE)	NE	12.9 (7.1–NE)
Median PFS, mo (95% CI)	11.2 (8.0–14.9)	7.7 (4.7–NE)	12.0 (8.7–15.7)

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

Doebele RC, et al. *Lancet Oncol*. 2020;21:271-282.

Entrectinib in Adult Patients
Marked and Durable Antitumor Activity

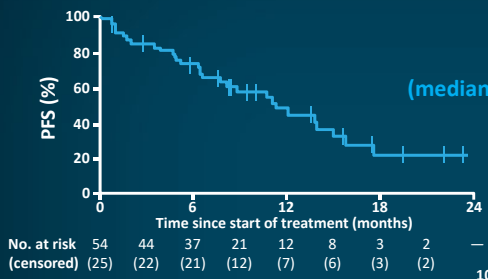


Median duration of response = 10 months

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

Doebele RC, et al. *Lancet Oncol*. 2020;21:271-282.

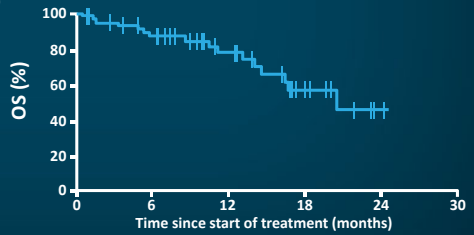
Entrectinib in Adult Patients
Secondary Outcomes



No. at risk (censored)									
	54	44	37	21	12	8	3	2	—
	(25)	(22)	(21)	(12)	(7)	(6)	(3)	(2)	

PFS
(median = 11 months)

OS
(median = 21 months)



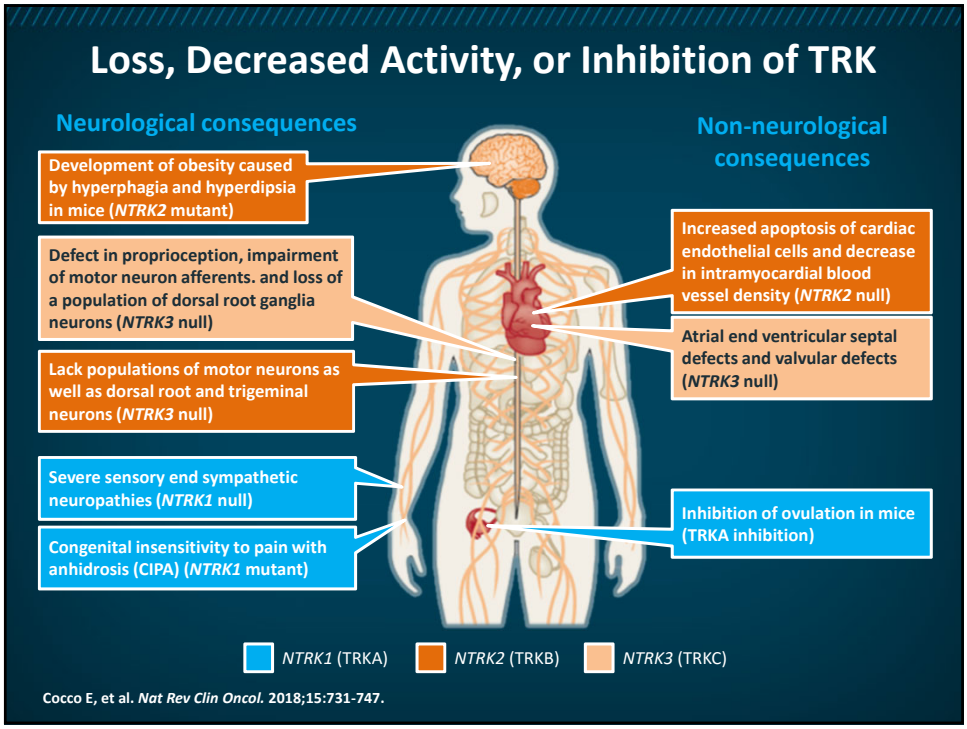
No. at risk (censored)											
	54	48	42	33	22	16	9	4	1	—	—
	(38)	(35)	(33)	(25)	(16)	(13)	(8)	(4)	(1)		

OS = overall survival.

Doebele RC, et al. *Lancet Oncol*. 2020;21:271-282.

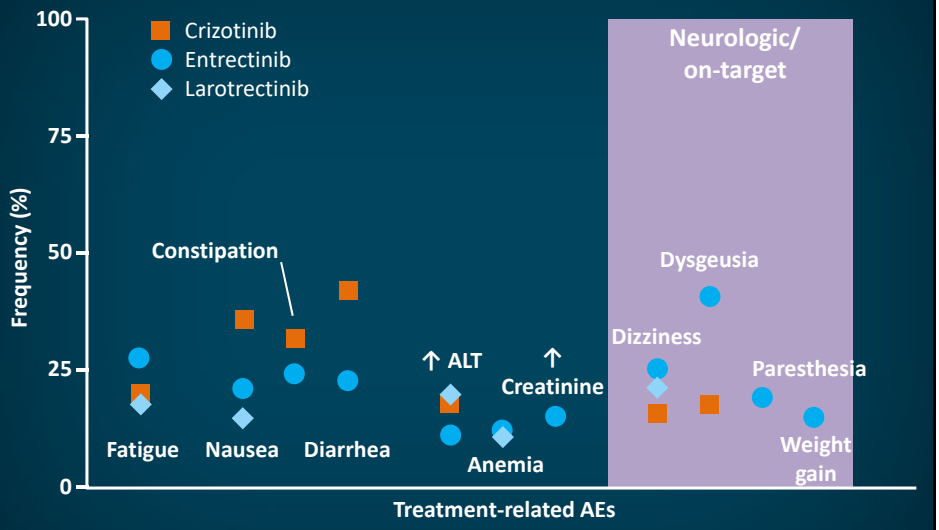
Targeted Therapy: On-Target Side-Effects

Loss, Decreased Activity, or Inhibition of TRK



Cocco E, et al. *Nat Rev Clin Oncol.* 2018;15:731-747.

Select Adverse Events: Entrectinib/Larotrectinib*

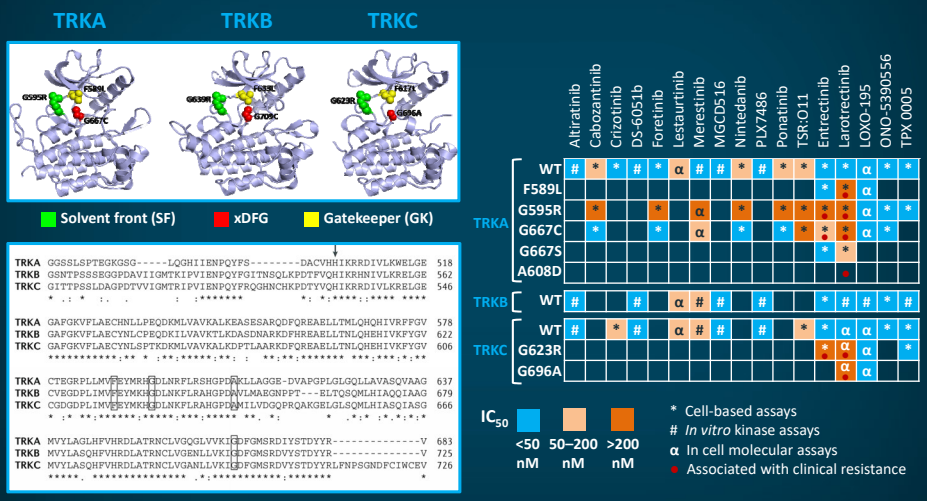


*To benchmark frequency of AEs, crizotinib, which has well-known safety profile, was chosen for comparison.
AE = adverse event; ALT = alanine aminotransferase.

Drilon A. *Ann Oncol*. 2019;30(suppl 8):viii23-viii30.

Resistance and Sequential TKI Therapy

First-Generation TRK Inhibitor Resistance Can Be Mediated By On-Target Mechanisms



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

Modified from Cocco E, et al. *Nat Rev Clin Oncol.* 2018;15:731-747.

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*

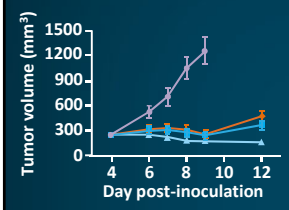
TKI = tyrosine kinase inhibitor; LMW = low molecular weight.

Drilon A, et al. *Cancer Discov.* 2018;8:1227-1236.

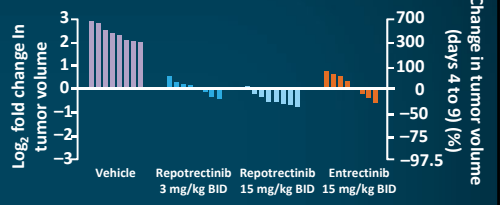
***Not approved by the FDA**

Repotrectinib*: Efficacy in NIH303 LMNA TRKA WT and G595R Tumors *ROS1/TRK/ALK* Inhibitor

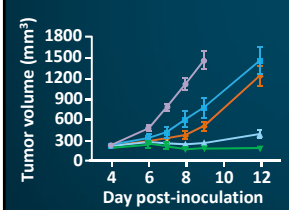
Antitumor activity of repotrectinib in NIH3T3 LMNA-TRKA WT tumors



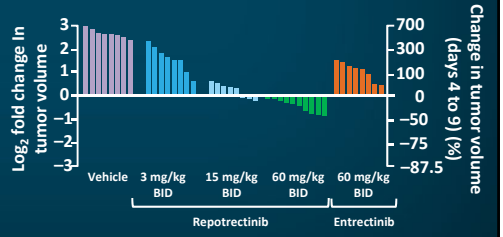
	TGI
Vehicle BID	
Repotrectinib 3 mg/kg BID	100%
Repotrectinib 15 mg/kg BID	128%
Entrectinib 3 mg/kg BID	98%



Antitumor activity of repotrectinib in NIH3T3 LMNA-TRKA^{G595R} tumors



	TGI
Vehicle BID	
Repotrectinib 3 mg/kg BID	56%
Repotrectinib 15 mg/kg BID	97%
Repotrectinib 60 mg/kg BID	123%
Entrectinib 3 mg/kg BID	78%

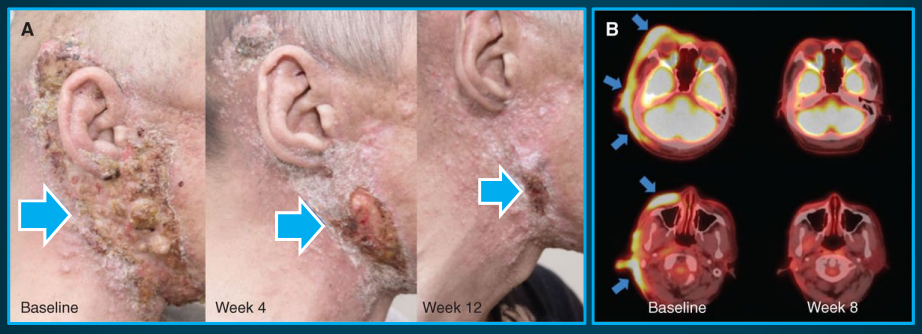


BID = twice daily; TGI = tumor growth inhibition.

*Not approved by the FDA

Drilon A, et al. *Cancer Discov.* 2018;8:1227-1236.

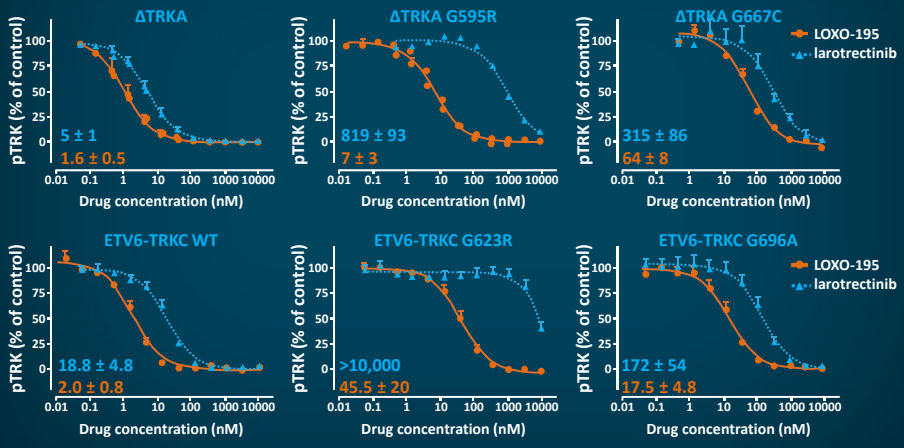
ETV6-NTRK3-Rearranged MASC With *NYRK3*^{G623E}-Mediated Resistance to Entrectinib



Drilon A, et al. *Cancer Discov.* 2018;8:1227-1236.

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.

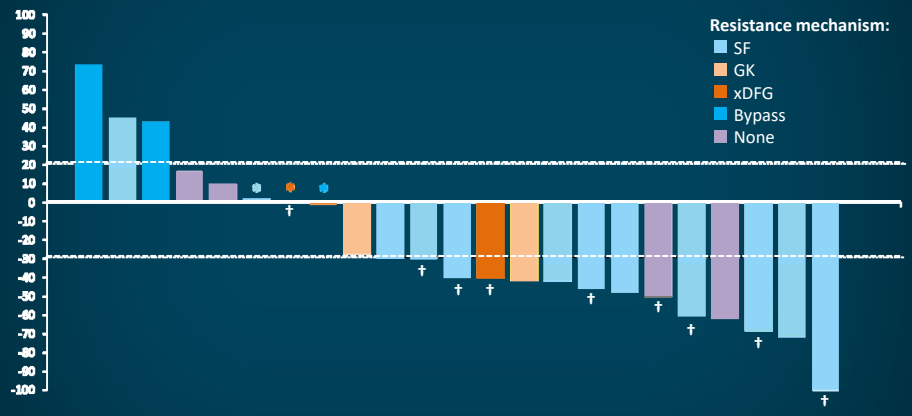


ELISA = enzyme-linked immunosorbent assay; Δ = change in.

Drilon A, et al. *Cancer Discov*. 2017;7:963-972.

*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.

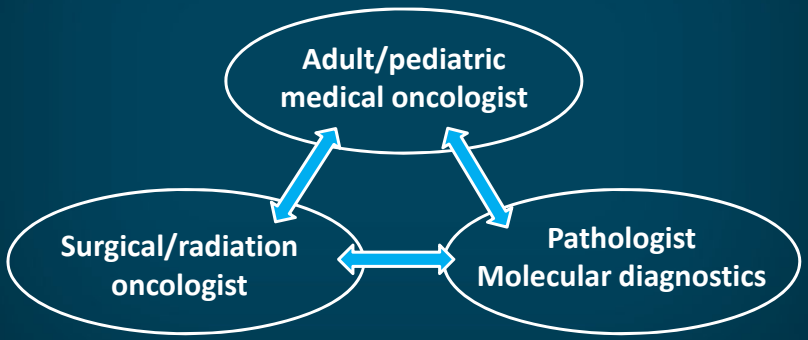
Hyman D, et al. Abstract CT127. *AACR* Annual Meeting; April 1, 2019.

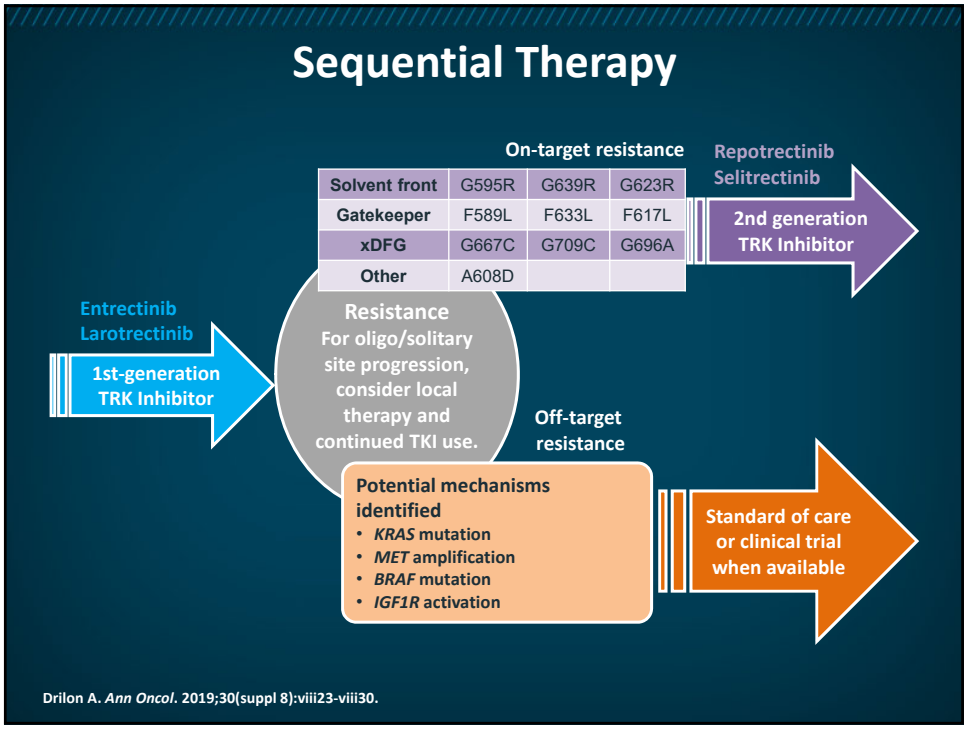
*Not approved by the FDA

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.





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.

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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*.

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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.

Solomon JP, et al. *Mod Pathol*. 2020;33:38-46.

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Solomon JP, et al. *Mod Pathol*. 2020;33:38-46.

Case Two: Presentation

- A 42-year-old female with widely metastatic melanoma is found to harbor an *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 **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 *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 *NTRK1* 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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Solomon JP, et al. *Mod Pathol*. 2020;33:38-46.

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.

Solomon JP, et al. *Mod Pathol*. 2020;33:38-46.

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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

Cocco E, et al. *Nat Rev Clin Oncol*. 2018;15:731-747.

Electronic Evaluation Form

- Before we move to Q&A, I want to remind you to fill out your evaluation form electronically.
- Once you complete your evaluation form, your CME certificate will be provided as a PDF that you can save for your records.
- You will also have the opportunity to download a PDF of the program slides.
- Even if you do not need credit, we appreciate you completing the evaluation form.

Thank You!

TRK Fusion-Positive Cancer: Identification, Diagnosis and Management

Resource	Address
Benayed R, et al. High Yield of RNA Sequencing for Targetable Kinase Fusions in Lung Adenocarcinomas with No Mitogenic Driver Alteration Detected by DNA Sequencing and Low Tumor Mutation Burden. *Clin Cancer Res*. 2019;25(15):4712-4722.	https://www.ncbi.nlm.nih.gov/pubmed/31028088
Cocco E, et al. NTRK fusion-positive cancers and TRK inhibitor therapy. *Nat Rev Clin Oncol*. 2018;15(12):731-747.	https://www.ncbi.nlm.nih.gov/pubmed/30333516
Doebele R, et al. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1-2 trials. *Lancet Oncol*. 2020;21(2):271-282.	https://www.ncbi.nlm.nih.gov/pubmed/31838007
Drilon A, et al. Efficacy of Larotrectinib in TRK Fusion-Positive Cancers in Adults and Children. *N Engl J Med*. 2018;378(8):731-739.	https://www.ncbi.nlm.nih.gov/pubmed/29466156
Drilon A, et al. Repotrectinib (TPX-0005) Is a Next-Generation ROS1/TRK/ALK Inhibitor That Potently Inhibits ROS1/TRK/ALK Solvent- Front Mutations. *Cancer Discov*. 2018;8(10):1227-1236.	https://www.ncbi.nlm.nih.gov/pubmed/30093503
Drilon A. TRK inhibitors in TRK fusion-positive cancers. *Ann Oncol*. 2019;30(Suppl 8):viii23-viii30.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6859818/
Hechtman JF, et al. Pan-Trk Immunohistochemistry Is an Efficient and Reliable Screen for the Detection of NTRK Fusions. *Am J Surg Pathol*. 2017;41(11);1547-1551.	https://www.ncbi.nlm.nih.gov/pubmed/28719467
Hong DS, et al. Larotrectinib in patients with TRK fusion-positive solid tumours: a pooled analysis of three phase 1/2 clinical trials. *Lancet Oncol*. 2020;21(4):531-540.	https://www.ncbi.nlm.nih.gov/pubmed/32105622

Lassen U. How I treat *NTRK* gene fusion-positive cancers. *ESMO Open*. 2019;4(Suppl 2):e000612.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6890394/
Mamdani H, et al. Breakthroughs and challenges in the management of tropomyosin receptor kinase fusion-positive tumors. *Ann Transl Med.* 2019;7(Suppl 3):S155.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6685873/
Marchiò C, et al. ESMO recommendations on the standard methods to detect NTRK fusions in daily practice and clinical research. *Ann Oncol*. 2019;30(9):1417-1427.	https://www.ncbi.nlm.nih.gov/pubmed/31268127
Penault-Llorca F, et al. Testing algorithm for identification of patients with TRK fusion cancer. *J Clin Pathol*. 2019;72(7):460–467.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6589488/
Solomon JP, et al. Identifying patients with *NTRK* fusion cancer. *Ann Oncol*. 2019;30(Suppl 8):viii16–viii22.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6859817/
Soloman JP, et al. NTRK fusion detection across multiple assays and 33,997 cases: diagnostic implications and pitfalls. *Mod Pathol*. 2020;33(1):38-46.	https://www.ncbi.nlm.nih.gov/pubmed/31375766

Resources and Societies

Resource	Address
American Association for Cancer Research	https://www.aacr.org/
American Cancer Society	https://www.cancer.org/
American Society of Clinical Oncology	https://www.asco.org/
National Cancer Institute	https://www.cancer.gov/
National Comprehensive Cancer Network - Guidelines	https://www.nccn.org/professionals/physician_gls/default.aspx