
NTRK
connect®
POWERED BY COR2ED

EXPERTS KNOWLEDGE SHARE

CURRENT OPINIONS ON HOW TO IDENTIFY, TEST AND TREAT *NTRK* FUSION POSITIVE CANCER

Prof. David Hong, Prof. Frédérique Penault-Llorca
and Prof. Ezra Cohen

20th January 2021

EXPERTS KNOWLEDGE SHARE

NTRK connect®
POWERED BY COR2ED

THE OBJECTIVE OF THIS MEETING IS TO SHARE CURRENT OPINIONS ON HOW TO IDENTIFY, TEST AND TREAT *NTRK* FUSION POSITIVE CANCER

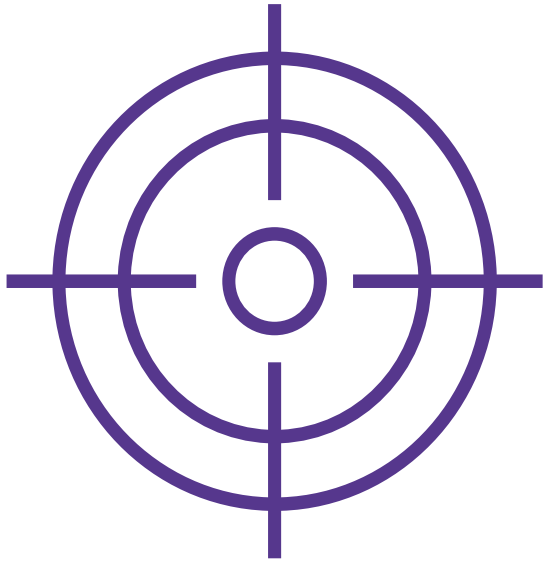
YOUR OPPORTUNITY TO **DISCUSS AND SHARE LEARNINGS** ON CHALLENGING TOPICS WITHIN THE AREA OF *NTRK* FUSION POSITIVE CANCER

A CHANCE TO HEAR THE **VIEWS OF EXPERTS** AND ALLOW THEM TO ANSWER THE QUESTIONS THAT ARE IMPORTANT TO YOU

REVIEW AND DISCUSS **PATIENT CASE STUDIES**, USING THE QUESTIONS THAT YOU HAVE SENT IN ADVANCE OF THIS EVENT

EXPERTS KNOWLEDGE SHARE EDUCATIONAL OBJECTIVES

NTRK connect®
POWERED BY COR2ED



To discuss current opinions on how to identify, test and treat *NTRK* fusion positive cancer:

- Treating *NTRK* fusion cancer today and in the future
- Testing methodologies and tumour-specific algorithms
- Adverse events associated with TRK inhibitors

INTRODUCING THE SCIENTIFIC COMMITTEE

NTRK connect®
POWERED BY COR2ED

David Hong

University of Texas MD Anderson Cancer Center, Houston, USA

Frédérique Penault-Llorca

University of Clermont-Ferrand, France

Ezra Cohen

UC San Diego Health-Moores Cancer Centre California, USA

DISCLAIMER

This meeting is based on an independent medical educational grant from Bayer. The programme is therefore independent; the content is not influenced by Bayer and is the sole responsibility of the experts

Please note:

The views expressed within this presentation are the personal opinions of the experts. They do not necessarily represent the views of the experts' academic institutions or the rest of the faculty

EXPERTS KNOWLEDGE SHARE AGENDA

NTRK connect®
POWERED BY COR2ED

Time	Topic	Facilitator
5 minutes	Welcome and introductions	Iain Murdoch (COR2ED)
5 minutes	Overview and scene setting	David Hong
15 minutes	Treating *NTRK* fusion cancer today	David Hong
15 minutes	Testing methodologies and tumour-specific algorithms	Frédérique Penault-Llorca
15 minutes	Adverse events associated with TRK inhibitors	Ezra Cohen
30 minutes	Two breakout rooms Groups discussing questions, case studies and sharing experiences	All
5 minutes	A look to future treatments and closing remarks	David Hong and Iain Murdoch (COR2ED)

TREATING *NTRK* FUSION CANCERS TODAY

David S. Hong, MD

The University of Texas MD Anderson Cancer Center.
Professor
Deputy Chairman in the Dept of Investigational Cancer Therapeutics
(Phase 1 Program)
Associate Vice President of Clinical Research

DISCLOSURES (LAST 36 MONTHS)

Research/Grant Funding: AbbVie, Adaptimmune, Aldi-Norte, Amgen, AstraZeneca, 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, Numab, Pfizer, Seattle Genetics, Takeda, Turning Point Therapeutics, Verstatem

Travel, Accommodations, Expenses: Bayer, LOXO, miRNA, Genmab, AACR, ASCO, SITC

Consulting, Speaker or Advisory Role: Alpha Insights, Acuta, Amgen, Axiom, Adaptimmune, Baxter, Bayer, Boxer Capital, COG, Ecor1, Genentech, GLG, Group H, Guidepoint, HCW Precision, Infinity, Janssen, Merrimack, Medscape, Numab, Pfizer, Prime Oncology, Seattle Genetics, ST Cube, Takeda, Tavistock, Trieza Therapeutics, WebMD

Other ownership interests: Molecular Match (Advisor), OncoResponse (Founder), Presagia Inc (Advisor)

TRK BIOLOGY

TRK, tropomyosin receptor kinase

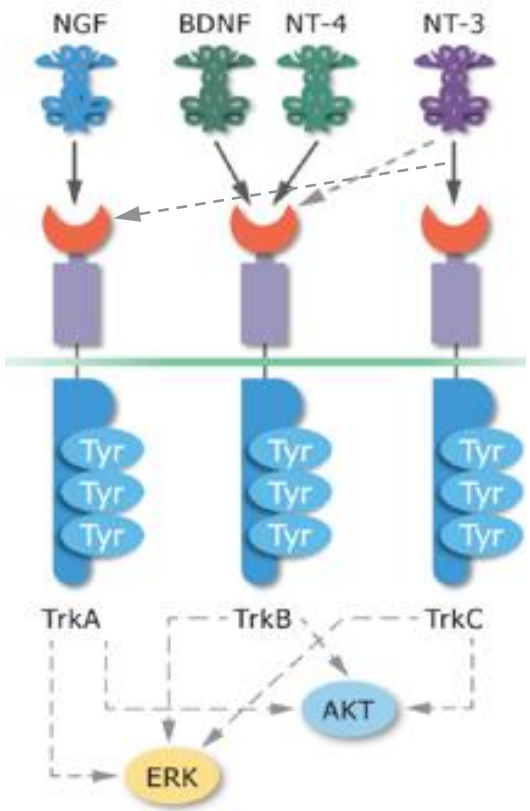
TRK RECEPTORS MEDIATE NEUROTROPHIN SIGNALLING

- Neurotrophins are important growth factors that promote sympathetic nervous system development[1,2]
- Neurotrophin signalling occurs through activation of the tropomyosin-receptor kinase (TRK) receptor family[1,2]

Neurotrophin Family of Receptors[1–6]

TRK Receptor	Gene (Chromosomal Location)	Functions	Natural Ligands
TRKA	*NTRK1* (1q23.1)	Pain signaling, thermoregulation	Nerve growth factor (NGF), neurotrophin-3 (NT-3)
TRKB	*NTRK2* (9q21.33)	Regulation of movement, memory, mood, appetite, body weight	Brain-derived neurotrophic factor (BDNF), neurotrophin-4 (NT-4), NT-3
TRKC	*NTRK3* (15q25.3)	Proprioception	NT-3

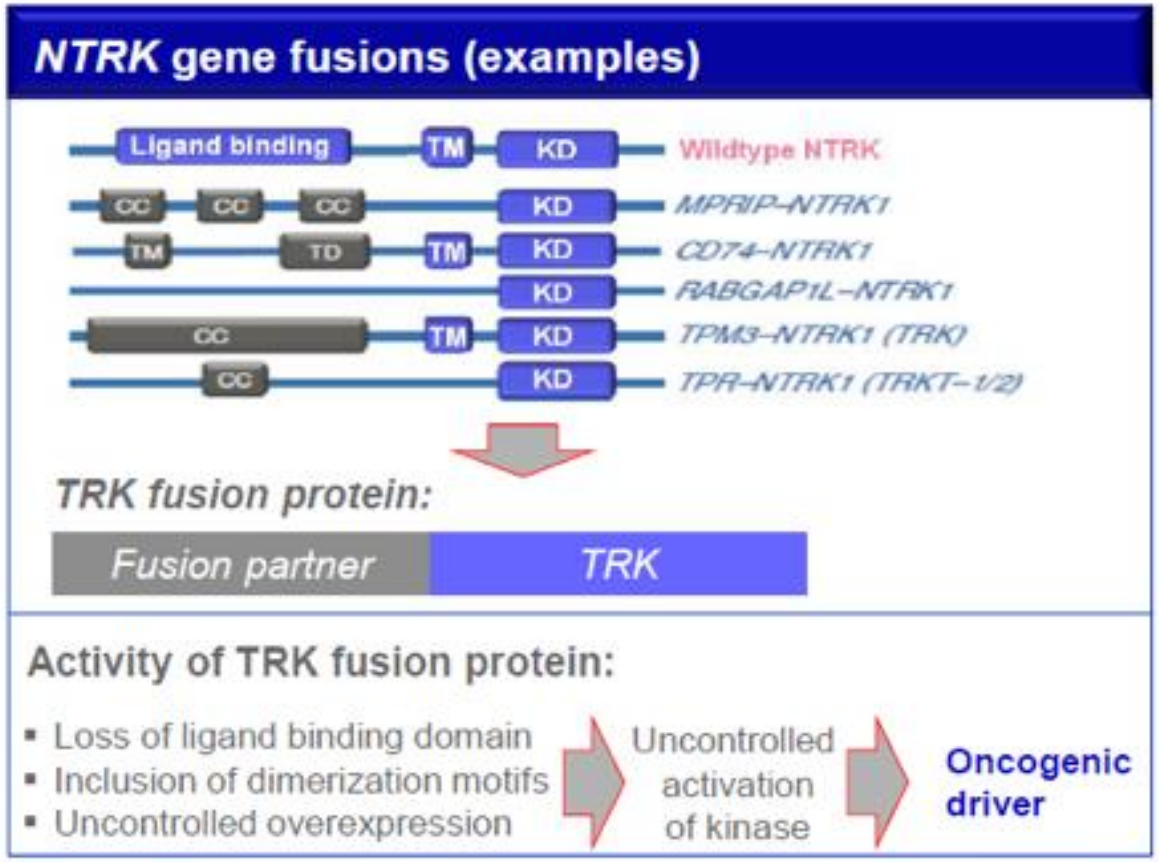
Neurotrophin signalling[1,3]

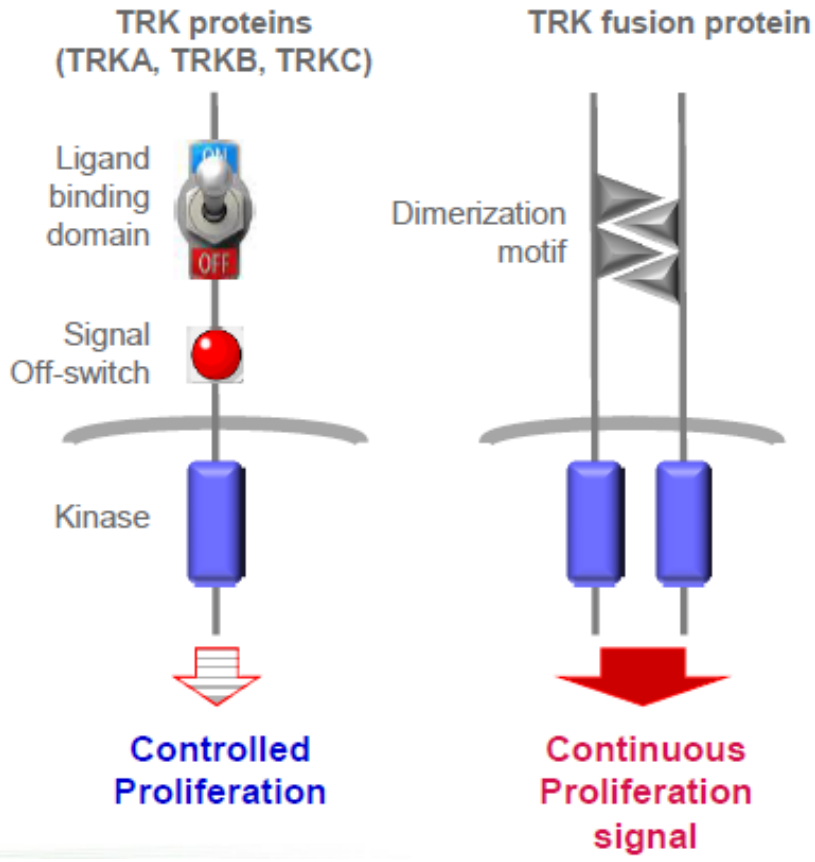


AKT, protein kinase B; ERK, extracellular signal-regulated kinase; NTRK, neurotrophic tyrosine receptor kinase; TRK, tropomyosin receptor kinase; Tyr, tyrosine

1. Nakagawara A. Cancer Lett. 2001;169:107-14; 2. Vaishnavi A, et al. Cancer Discov. 2015;5:25-34; 3. Blake J, et al. EORTC-NCI-AACR Conf. 2016;69:ENA-0491/ Poster No. 442; 4. https://www.ncbi.nlm.nih.gov/gene/4914, accessed January 17, 2021; 5. https://www.ncbi.nlm.nih.gov/gene/4915, accessed January 17, 2021; 6. https://www.ncbi.nlm.nih.gov/gene/4916, accessed January 16, 2021

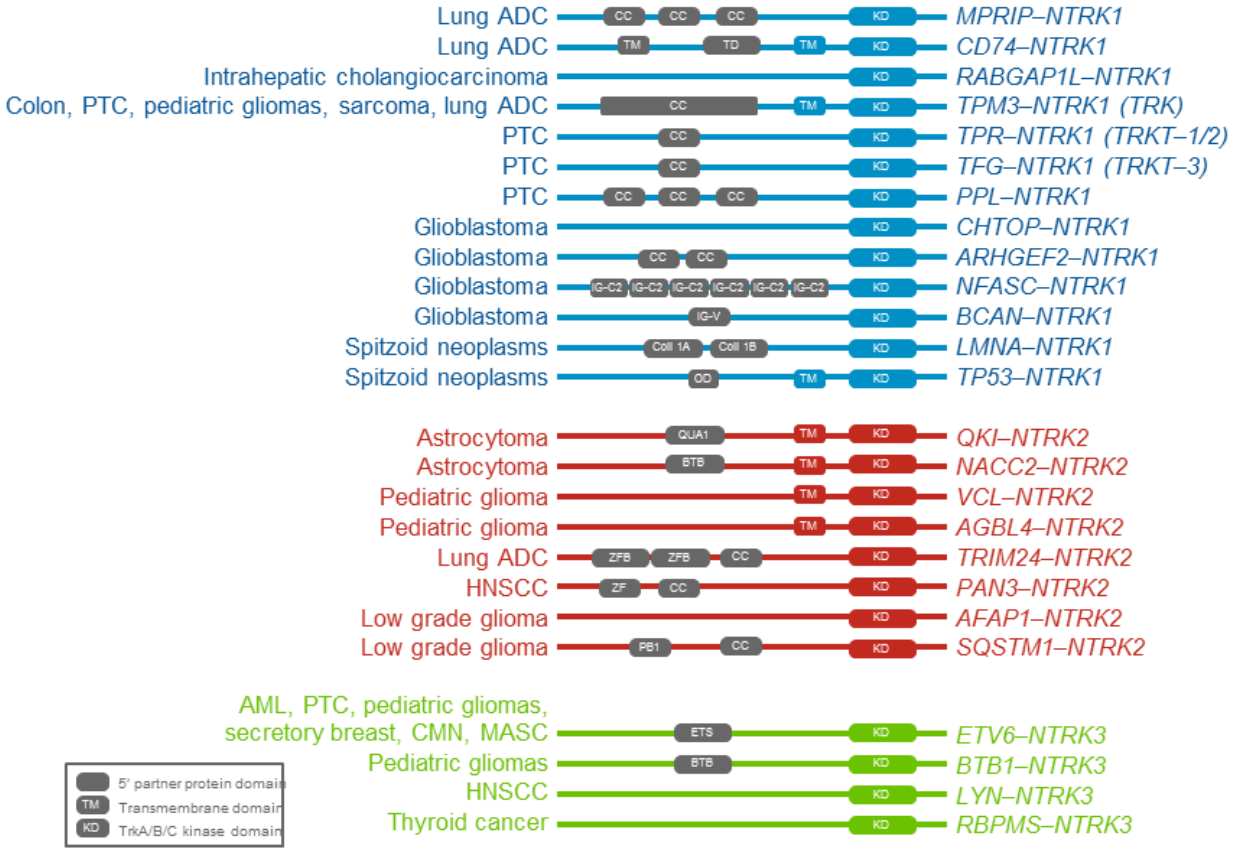
BIOLOGY OF TRK FUSION PROTEINS





CC, coiled coil domain; KD, kinase domain; NTRK, neurotrophic tyrosine receptor kinase; TD; trimerisation domain: TM, transmembrane domain; TRK, tropomyosin receptor kinase

THERE ARE NUMEROUS *NTRK* GENE FUSION TYPES ACROSS MULTIPLE TUMOUR TYPES



- There are a number of known *NTRK1* (blue), *NTRK2* (red), and *NTRK3* (green) fusions and tumours types in which they have been identified
- Not all gene fusions have been characterised functionally
- Novel/non-canonical fusions are common, including in IFS

ADC, adenocarcinoma; AML, acute myeloid leukaemia; BTB, bric-a-brac, tram-track, and broad complex domain; CCD, coiled-coil domain; CMN, congenital mesoblastic nephroma; ETS, E26 transformation-specific domain; HNSCC, head and neck squamous cell cancer; IFS, infantile fibrosarcoma; IG-C2, immunoglobulin-like C2-type domain; IG-V, immunoglobulin-like V domain; KD, kinase domain; MASC, mammary analogue secretory carcinoma; NTRK, neurotrophic tyrosine receptor kinase; OD, oligomerization domain; PTC, papillary thyroid cancer; TD, trimerization domain; TM, transmembrane domain; ZF, Zinc finger domain; QUA1, quaking 1 domain

Vaishnavi A, et al. Cancer Discov. 2015;5:25-34

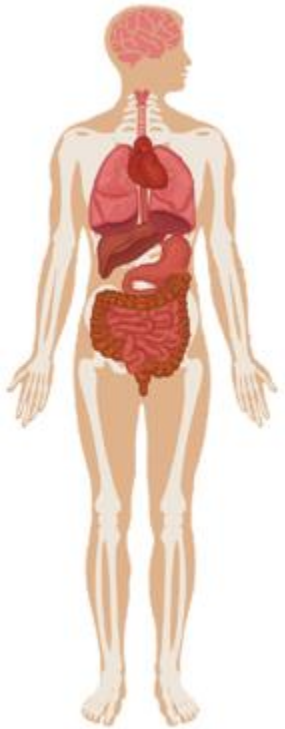
TRK CANCER EPIDEMIOLOGY

TRK, tropomyosin receptor kinase

NTRK GENE FUSIONS ARE FOUND IN MANY CANCERS WITH HIGH UNMET NEED

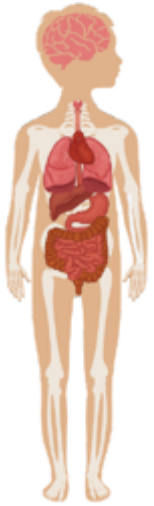
NTRK connect® POWERED BY COR2ED

Adult



- Brain cancers (0.4–3.1%)[1]
- Salivary (MASC; 90–100%)[1]
- Secretory breast cancer (92%)[2*]
- Pancreatic cancer[3]
- Cholangiocarcinoma (3.6%)[1]
- Thyroid cancer (1.5–14.5%)[1]
- Lung cancer (0.2–3.3%)[1]
- GIST (3.2%)[4]
- Colon cancer (1.5%)[1]
- Melanoma (0.3%)[1,5]
- Sarcomas (1%)[5*]

Paediatric



- Spitzoid neoplasms (16.4%)[6]
- Gliomas (7.1%)[1]
- Thyroid (9.4–25.9%)[7,8]
- Infantile fibrosarcoma (91–100%)[9]
- Congenital nephroma (83%)[1]
- Secretory breast cancer (92%)[2*]
- Sarcomas (1%)[5a]

1. Vaishnavi A, Le A, Doebele RC. *Cancer Discov.* 2015;5:25-34.
2. Tognon C, et al. *Cancer Cell*. 2002;2:367-376.
3. Pishvaian MJ, et al. *Journal of Clinical Oncology* 36, no. 4_suppl (February 1 2018) 521-521.
4. Brenca M, et al. *J Pathol* 2016;238:543-549.
5. Stransky N, et al. *Nat Communications* 2014;DOI: 10.1038/ncomms5846.
6. Wiesner T, et al. *Nat Communications* 2014;5:3116. doi:10.1038/ncomms4116.
7. Ricarte_Filho_JC, et al. *J Clin Invest* 2013;123:4935-4944.
8. Prasad ML, et al. *Cancer* 2016; DOI: 10.1002/cncr.29887.
9. Bourgeois JM, et al. Am J Surg Pathol 2000;*24: 937–946.*

[a]Frequency in adult vs paediatric patients not specified

GIST, gastrointestinal stromal tumour; MASC, mammary analogue secretory carcinoma; NTRK, neurotrophic tyrosine receptor kinase

TRK INHIBITORS

TRK, tropomyosin receptor kinase

TRK INHIBITORS AND CLINICAL DEVELOPMENT STATUS

NTRK connect® POWERED BY COR2ED

larotrectinib and entrectinib are the two currently approved TRK inhibitors*

Drug Name (Sponsor)	Molecular Targets	Development Stage and tumour Types
larotrectinib (Bayer)	*NTRK1-3*	Phase 1/2 in solid tumours in adults and adolescents (NCT02122913, NCT02637687, NCT02576431)
entrectinib (Roche/ Ignyta)[1]	*NTRK1-3, ALK, ROS1*	Phase 1/2 in solid tumours in adults (NCT02568267, NCT02097810, NCT02650401)
TSR-011 (Tesaro)[1]	*NTRK, ALK*	Phase 1/2 in solid tumours and lymphomas (NCT02048488)[a]
sitravatinib (MGCD516) (Mirati Therapeutics)[1]	*NTRK1-3, DDR2, MET, KIT, KDR, PDGFR*	Phase 2 in combination with nivolumab in NSCLC; advanced liposarcoma and other soft tissue sarcomas (NCT02954991, NCT02978859)
DS-6051b (Daiichi Sankyo)[1]	*NTRK1-3, ROS1*	Phase 1 in solid tumours (NCT02675491,[a] NCT02279433[a]); Status unknown; presented at ESMO 2017 but not mentioned in latest independent research materials[4]
merestinib (Eli Lilly)[1]	*NTRK1-3, MET, AXL, ROS1, MKNK2, FLT3, TEK, DDR1, DDR2*	Phase 1/2 in combination with LY2874455[b] in R/R AML; advanced/metastatic cancer; NSCLC and solid tumours; biliary tract cancers (NCT03125239,[c] NCT03027284, NCT02920996, NCT02711553)
cabozantinib (Exelexis)[1]	*NTRK, KDR, MET, RET, ROS1, KIT, FLT1,3,4, AXL*	Phase 2 in NSCLC (NCT01639508)
PLX7486 (Plexxikon)[1]	*NTRK1-3, CSF1R*	Phase 1 in solid tumours (NCT01804530)
TPX-0005 (TP Therapeutics)[2]	*NTRK1-3, ALK, ROS1*	Phase 1/2 in advanced solid tumours (NCT03093116)
ONO-7579 (Ono)[3]	*NTRK1-3*	Phase 1/2 in advanced solid tumours (NCT03182257)[a]

[a] Trial is terminated; [b] LY2874455 is an FGFR inhibitor; [c] Trial is completed

ALK, anaplastic lymphoma kinase; AML, acute myeloid leukemia; AXL, tyrosine-protein kinase receptor UFO; CSF1R, colony stimulating factor 1 receptor; DDR, discoidin domain-containing receptor; ESMO, European Society for Medical Oncology; FGFR, fibroblast growth factor receptor; FLT, fms related tyrosine kinase; KDR, kinase insert domain receptor; KIT, mast/stem cell growth factor receptor; MET, c-MET proto-oncogene; MKNK, MAP kinase-interacting serine/threonine-protein kinase; NSCLC, nonsmall-cell lung carcinoma; NTRK, neurotrophic tyrosine receptor kinase; PDGFR, platelet-derived growth factor receptors; R/R, relapsed/refractory; RET, rearranged during transfection proto-oncogene; ROS1, proto-oncogene tyrosine-protein 1; TEK, tunica interna endothelial cell kinase; TRK, tropomyosin receptor kinase

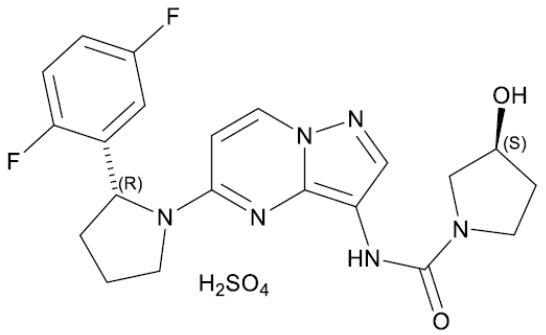
*Larotrectinib is approved in the US, Australia, Brazil, Canada, European Union, Hong-Kong, Israel, Saudi Arabia, Singapore, South Korea and Switzerland. Entrectinib is approved in the US, Australia, European Union and Japan

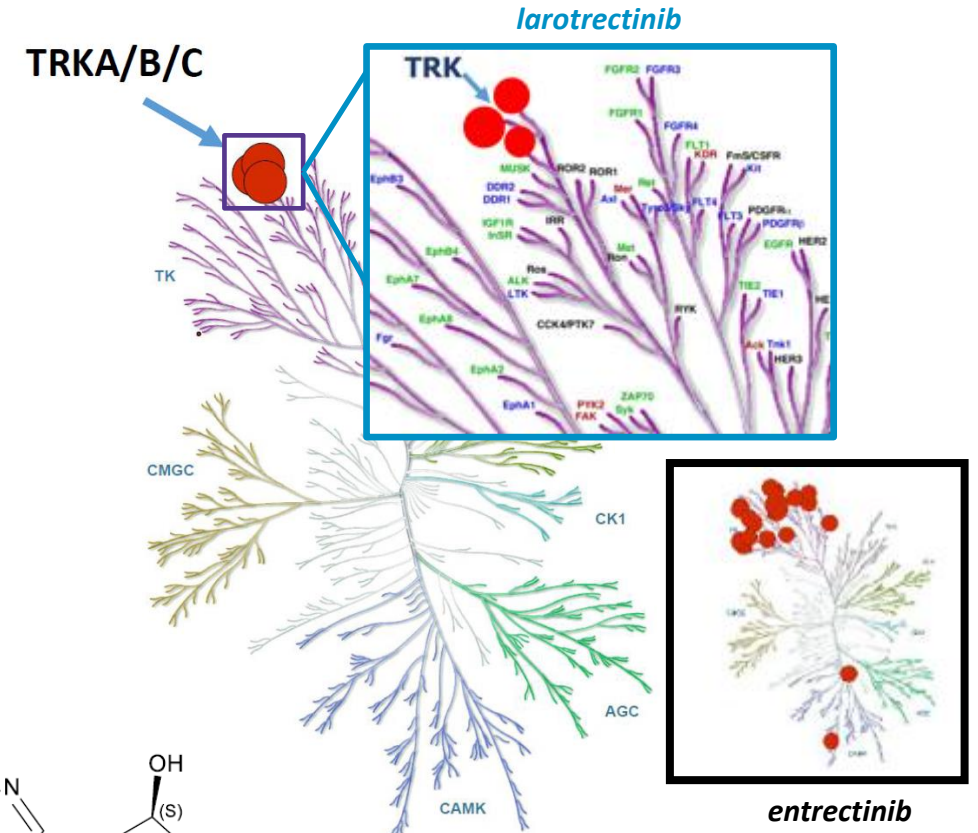
1. http://www.onclive.com/publications/oncology-live/2017/vol-18-no-15/trk-inhibitors-advance-rapidly-in-tumouragnostic-paradigm?p=2 (accessed January 16, 2021);
2. ClinicalTrials.gov. NCT03093116; 3. ClinicalTrials.gov. NCT03182257; 4. Takeda M, et al. Ann Oncol. 2017;28 (suppl_5):486-7

LAROTRECTINIB

LAROTRECTINIB IS A HIGHLY SELECTIVE TRK INHIBITOR

- First and only selective TRK inhibitor[1]
- High potency against TRKA, TRKB, and TRKC[1]
  - IC_{50} = 5-11 nM in cellular assays
- Slow dissociation; inhibitor stays bound to target[2]
  - $T_{1/2}$: 160 min
- High selectivity[1,2]
  - Limited inhibition of other kinases
  - ≥100-fold selectivity versus 229 other kinases

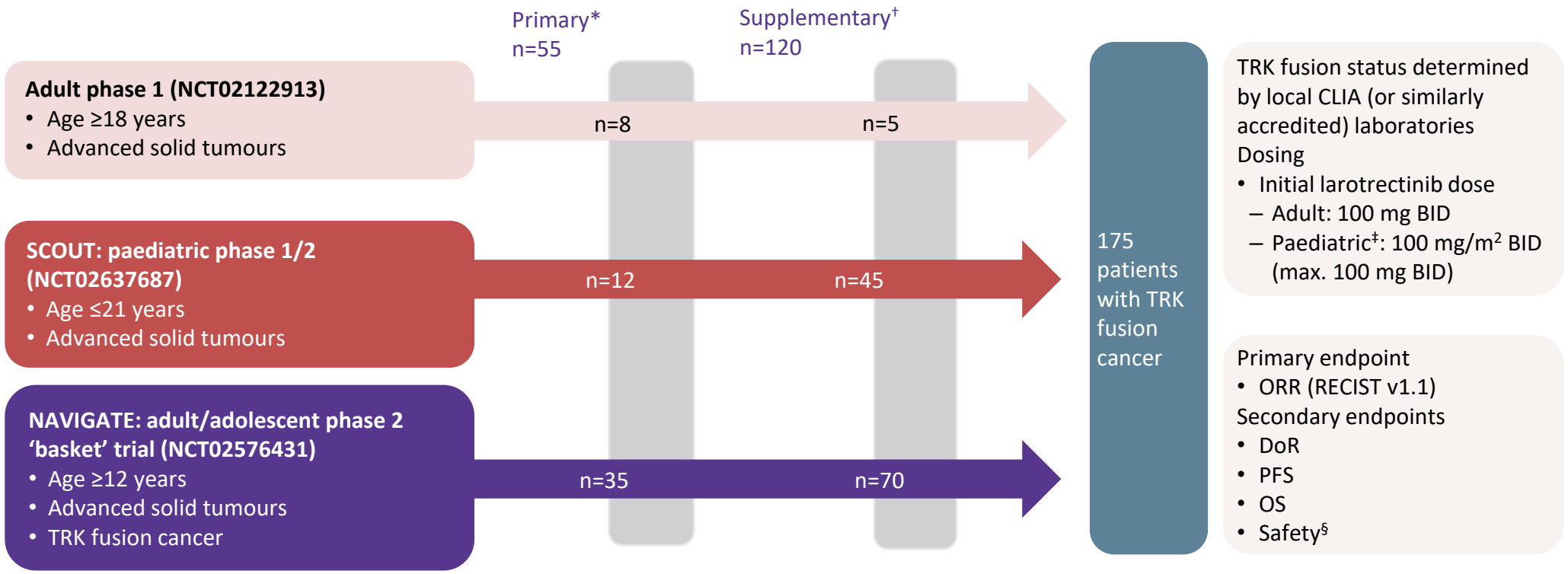




IC_{50}, half maximal inhibitory concentration; $T_{1/2}$, half-life; TRKA/B/C, tropomyosin receptor kinase A/B/C

1. Hyman DM, et al. J Clin Oncol. 2017;35:LBA2501; 2. Drilon A, et al. Ann Oncol. 2019;30 (suppl_8):viii23-viii30

LAROTRECTINIB CLINICAL DATA: INTEGRATED ANALYSIS STUDY DESIGN



* The primary dataset comprises the original patients included in the primary report with longer follow up

† The supplementary dataset comprises the additional patients included in this analysis

‡ The starting dose was determined by Simcyp® modelling, which predicted that the doses needed to match the larotrectinib exposure in adults given 100 mg BID are 9.6, 17, 28, 39, 49, 55, and 55 mg/m² for patients aged 1-3 months, 3-6 months, 6 months to 1 year, 1-2 years, 2-6 years, 6-12 years, and 12-18 years, respectively

§ The safety population included all patients enrolled in one of the three clinical trials, who received at least one dose of larotrectinib, regardless of TRK fusion status (n=279).

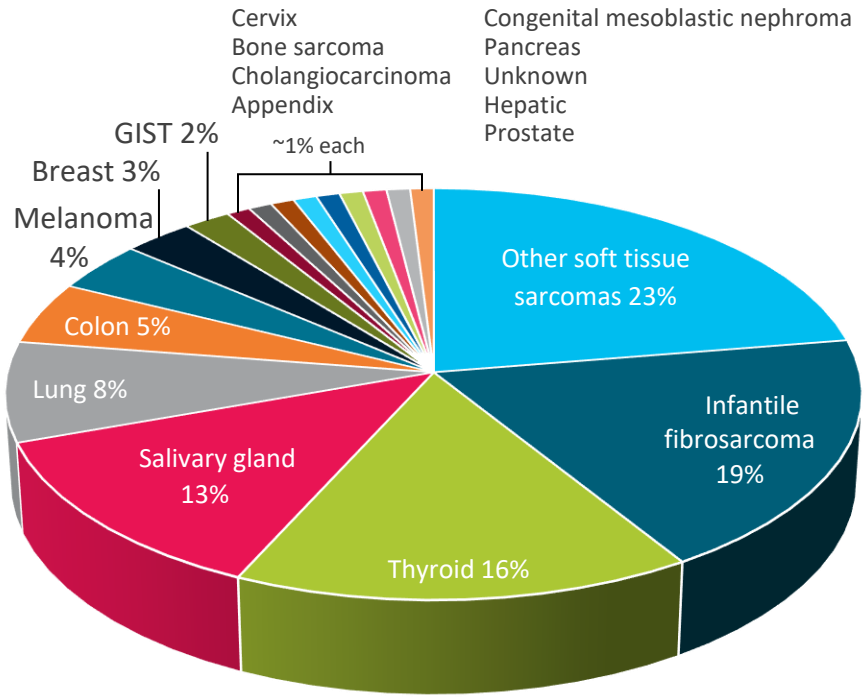
Data cut-off: July 15, 2019.

BID, twice daily; CLIA, Clinical Laboratory Improvement Amendments; DoR, duration of response; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumours; TRK, tropomyosin receptor kinase

McDermott R, et al. Ann Oncol. 2020;31 (suppl_4):S1034-S1051

LAROTRECTINIB CLINICAL DATA: INTEGRATED ANALYSIS BASELINE CHARACTERISTICS

	Integrated dataset (N=175)
Sex, n (%)	
Male	86 (49)
Female	89 (51)
Age, median (range), years	43 (0.1-84)
Paediatric (<18 years), n (%)	59 (34)
Adult (≥18 years), n (%)	116 (66)
ECOG PS, n (%)	
0	85 (49)
1	67 (38)
2	20 (11)
3	3 (2)
Known CNS metastases at enrollment, n (%)	14 (8)
Number of prior systemic therapies, median (range)	1 (1-10)
Number of prior systemic therapies, n (%)	
0	44 (25)
1	50 (29)
2	35 (20)
≥3	46 (26)
***NTRK* gene fusion, n (%)**	
NTRK1	72 (41)
NTRK2	6 (3)
*NTRK3**	97 (55)



Data cut-off: July 15, 2019

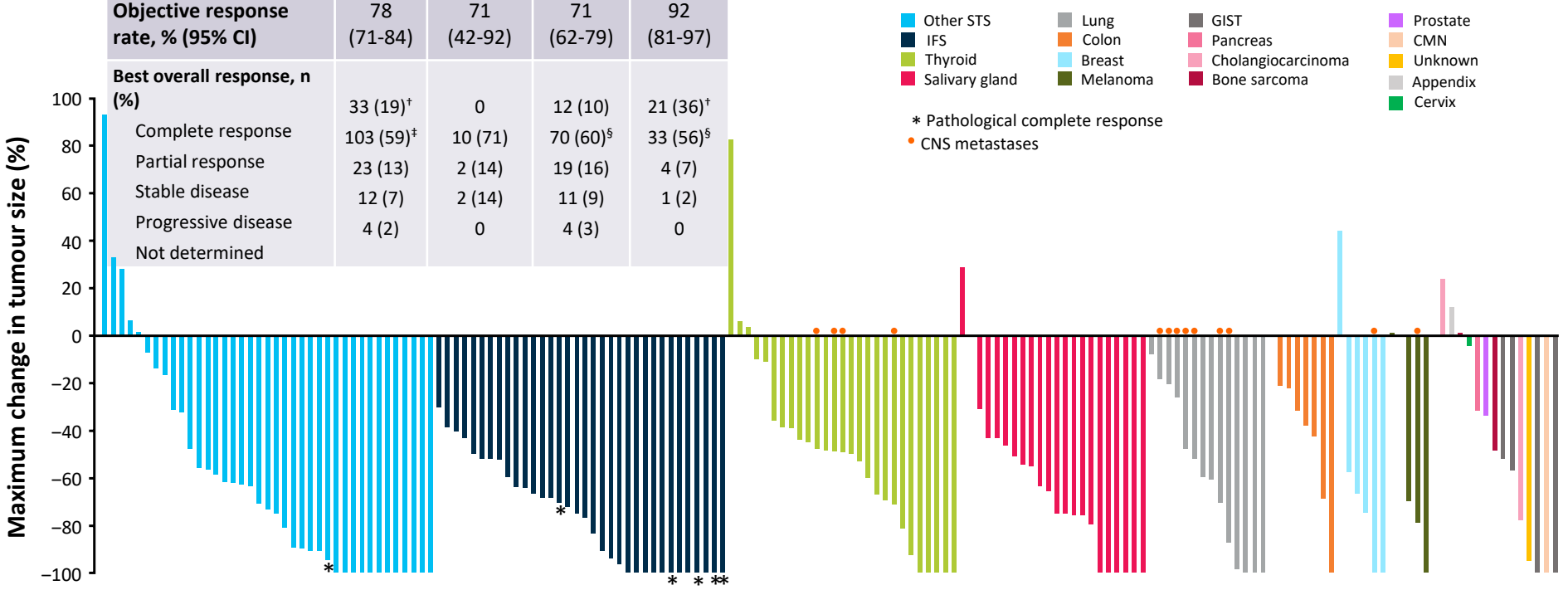
* Directly demonstrated or inferred (9 of 97 patients)

CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; GIST, gastrointestinal stromal tumour; NTRK, neurotrophic tyrosine receptor kinase

McDermott R, et al. Ann Oncol. 2020;31 (suppl_4):S1034-S1051

LAROTRECTINIB CLINICAL DATA: INTEGRATED ANALYSIS BEST RESPONSE BY TUMOUR TYPE

	Integrated dataset (N=175)	CNS metastases (n=14)	Adult patients (n=116)	Paediatric patients (n=59)
Objective response rate, % (95% CI)	78 (71-84)	71 (42-92)	71 (62-79)	92 (81-97)
Best overall response, n (%)				
Complete response	33 (19)†	0	12 (10)	21 (36)†
Partial response	103 (59)‡	10 (71)	70 (60)§	33 (56)§
Stable disease	23 (13)	2 (14)	19 (16)	4 (7)
Progressive disease	12 (7)	2 (14)	11 (9)	1 (2)
Not determined	4 (2)	0	4 (3)	0



Data cut-off: July 15, 2019

* Patients with a pathological complete response

† Including 6 patients with pathological complete response

‡ 4 partial responses pending confirmation

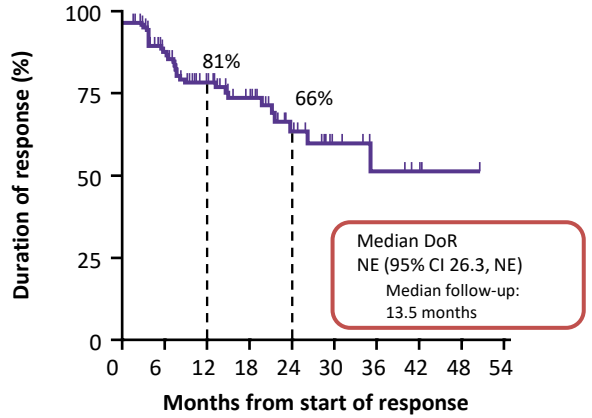
§ 2 partial responses pending confirmation

CI, confidence interval; CMN, congenital mesoblastic nephroma; CNS, central nervous system; GIST, gastrointestinal stromal tumour; IFS, infantile fibrosarcoma; STS, soft tissue sarcoma

McDermott R, et al. Ann Oncol. 2020;31 (suppl_4):S1034-S1051

LAROTRECTINIB CLINICAL DATA: INTEGRATED ANALYSIS DoR, PFS, AND OS

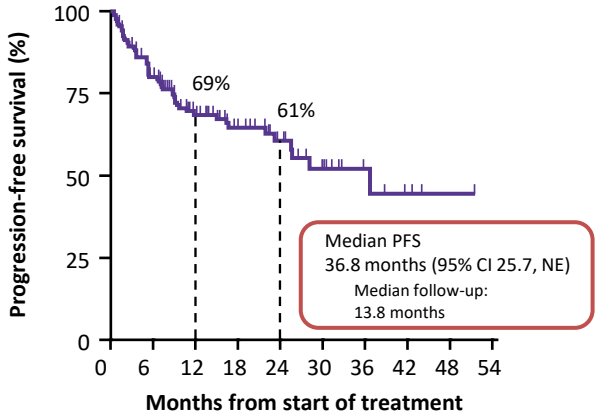
DoR



No. at risk 132 90 57 39 21 11 5 3 1 0

- Rate of ongoing response at 12 months: 81% (95% CI 73, 89)
- Rate of ongoing response at 24 months: 66% (95% CI 53, 78)

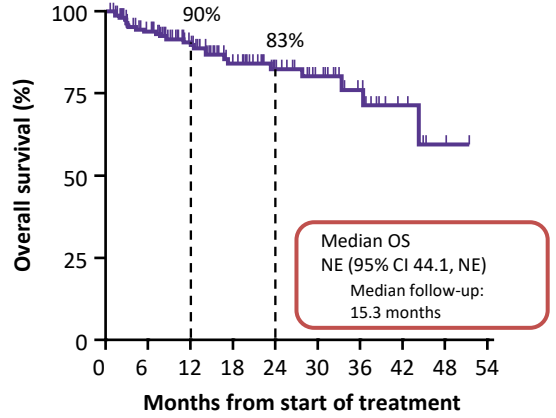
PFS



No. at risk 175 114 66 46 27 16 7 4 1 0

- PFS rate at 12 months: 69% (95% CI 61, 76)
- PFS rate at 24 months: 61% (95% CI 51, 70)

OS



No. at risk 175 114 93 64 43 30 17 7 2 0

- OS rate at 12 months: 90% (95% CI 85, 95)
- OS rate at 24 months: 83% (95% CI 75, 90)

- In 14 evaluable patients with brain metastases
  - Median DoR: 14.8 months (95% CI 3.7, NE) (median follow-up: 9.5 months)
  - Rate of ongoing response at 12 months: 61% (95% CI 26, 96)

Data cut-off: July 15, 2019

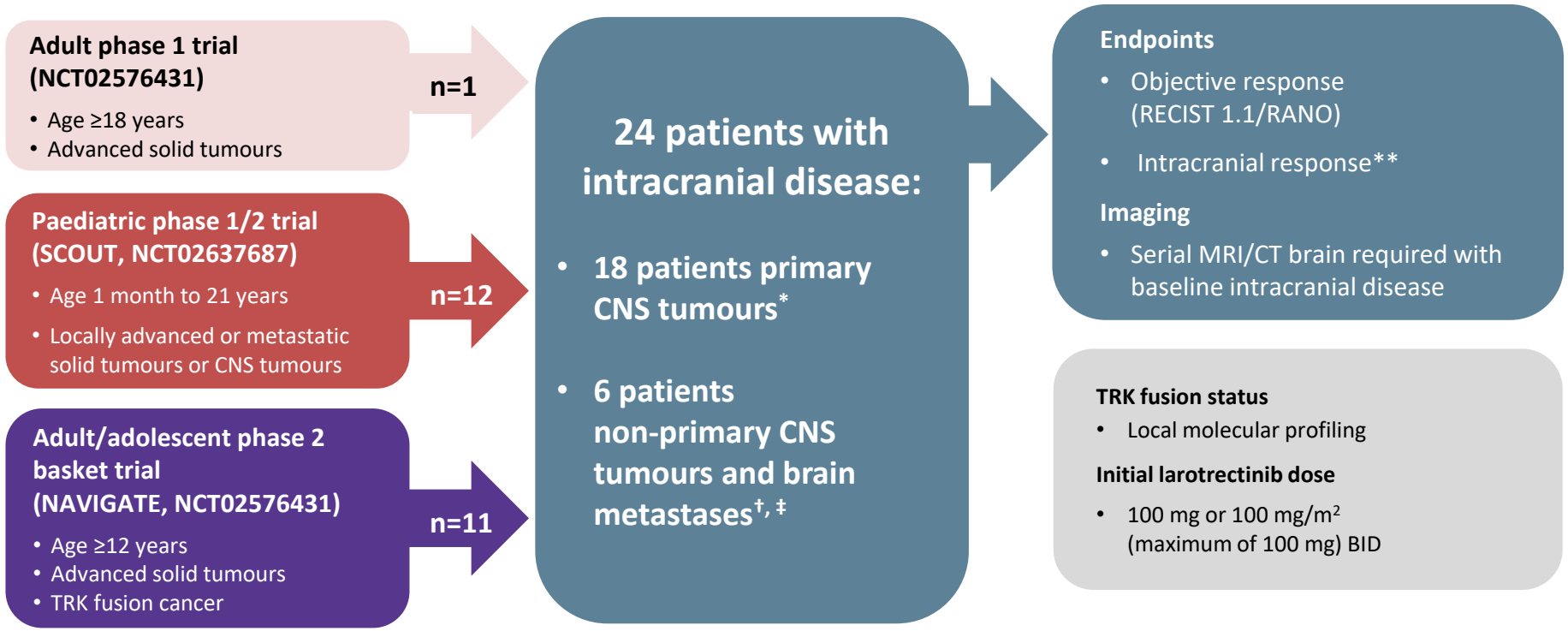
CI, confidence interval; DoR, duration of response; NE, not estimable; OS, overall survival; PFS, progression-free survival

McDermott R, et al. Ann Oncol. 2020;31 (suppl_4):S1034-S1051

LAROTRECTINIB IN INTRACRANIAL DISEASE: CHARACTERISTICS OF FIRST PROSPECTIVE ANALYSIS

NTRK connect® POWERED BY COR2ED

METHODS



* Data cut-off: February 19, 2019. † Data cut-off date July 30, 2018. ‡ Symptomatic or unstable brain metastases excluded. ** In tumour for patients with brain metastases; not a formal endpoint.

BID, twice daily; CNS, central nervous system; CT, computed tomography; MRI, magnetic resonance imaging; NTRK, neurotrophic tyrosine receptor kinase; RANO, response assessment in neuro-oncology; RECIST, Response Evaluation Criteria in Solid Tumours; TRK, tropomyosin receptor kinase

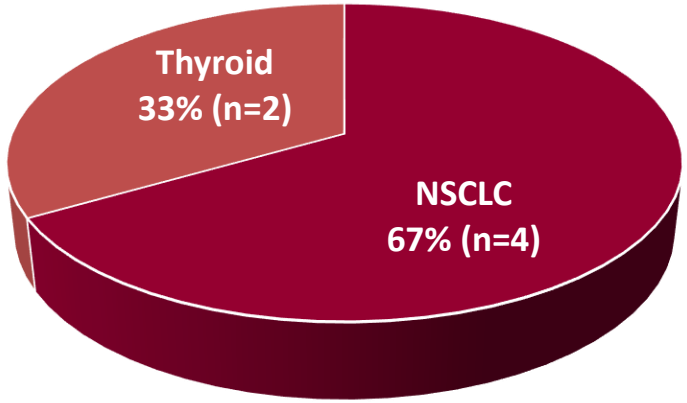
Drilon A, et al. J Clin Oncol. 2019;37 no. 15_suppl:2006-2006

LAROTRECTINIB IN INTRACRANIAL DISEASE: BASELINE CHARACTERISTICS IN PATIENTS WITH NON-PRIMARY CNS SOLID TUMOURS

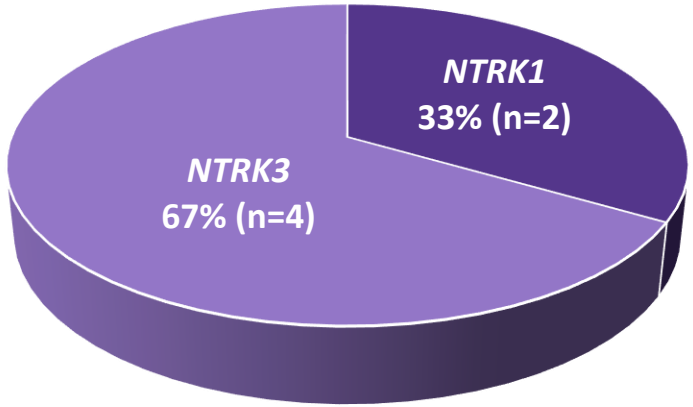
Frequency of brain metastases in TRK fusion-positive solid tumours: **5% (n=6/121)**

Characteristic	N=6
Gender, n (%) Female Male	 4 (67%) 2 (33%)
Age, median (range)	65 years (25-76)
Prior therapies, n (%) Systemic therapy Prior CNS Surgery/Radiotherapy Yes* No	5 (83%) 2 (33%) 4 (67%)
Number of prior systemic therapies, median (range)	2 (0-5)

Histology



Fusion



*2 patients received radiation for intracranial disease >1 year prior to larotrectinib, 1 of whom also underwent surgery for intracranial disease >1 year prior to larotrectinib

CNS, central nervous system; NSCLC, non-small cell lung cancer; NTRK, neurotrophic tyrosine receptor kinase; TRK, tropomyosin receptor kinase

Drilon A, et al. J Clin Oncol. 2019;37 no. 15_suppl:2006-2006

LAROTRECTINIB IN INTRACRANIAL DISEASE: RESPONSE IN PATIENTS WITH NON-PRIMARY CNS SOLID TUMOURS

Overall efficacy	Evaluable patients N=5
Objective response rate, median (95% CI)	**60% (15-95)**
Best objective response*, n (%)	
Partial response	3 (60%)**
Stable disease	2 (40%)
Progressive disease	0 (0%)

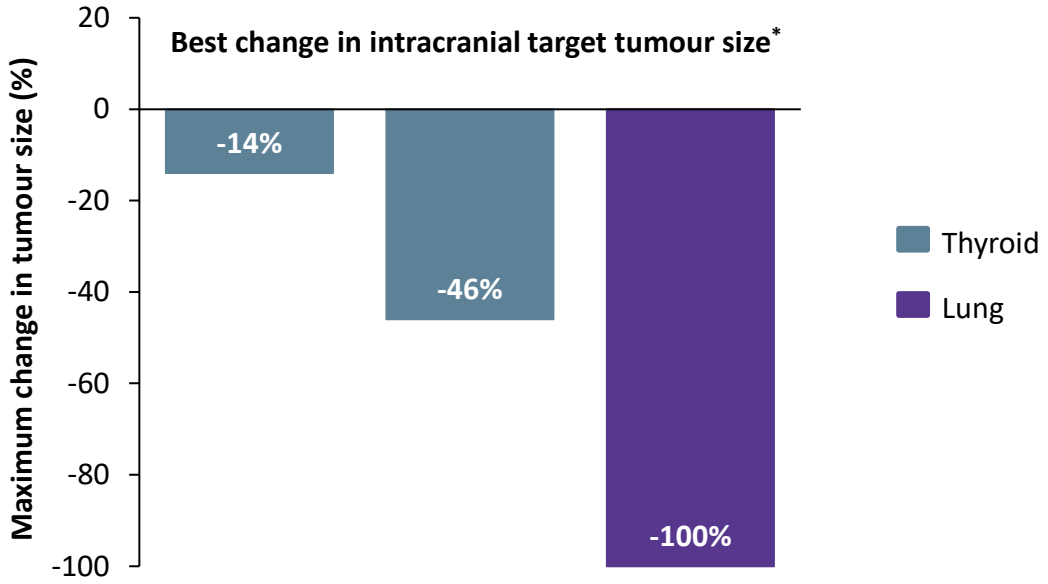
Data cut-off: July 30, 2018

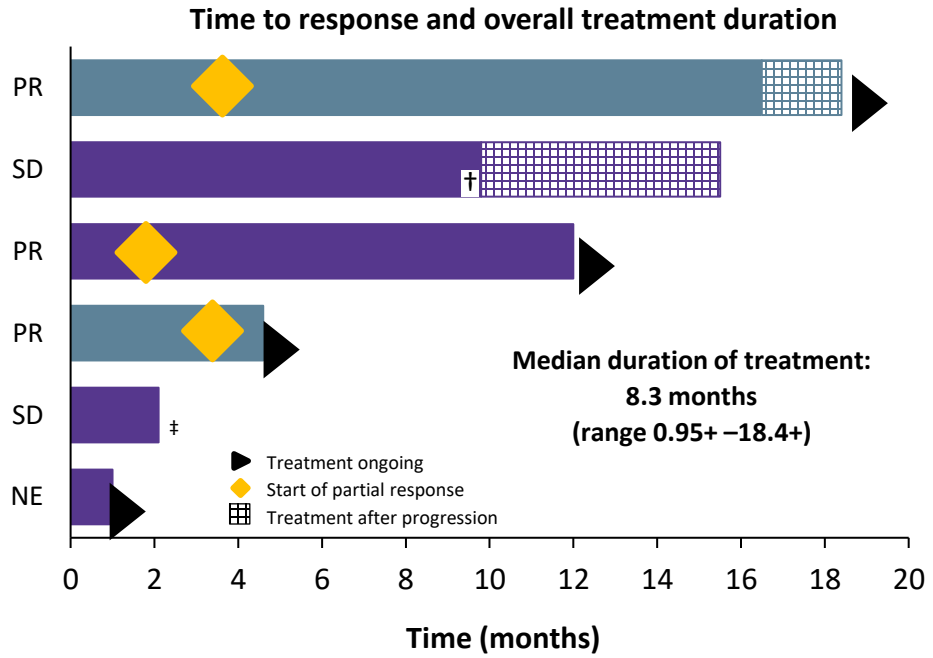
* Investigator assessment based on RECIST 1.1. **One patient pending confirmation

CI, confidence interval; NTRK, neurotrophic tyrosine receptor kinase; RECIST, Response Evaluation Criteria in Solid Tumours

Drilon A, et al. J Clin Oncol. 2019;37 no. 15_suppl:2006-2006

LAROTRECTINIB IN INTRACRANIAL DISEASE: RESPONSE/TREATMENT DURATION IN PATIENTS WITH NON-PRIMARY CNS SOLID TUMOURS





Data cut-off: July 30, 2018. Disease assessments were performed by investigators

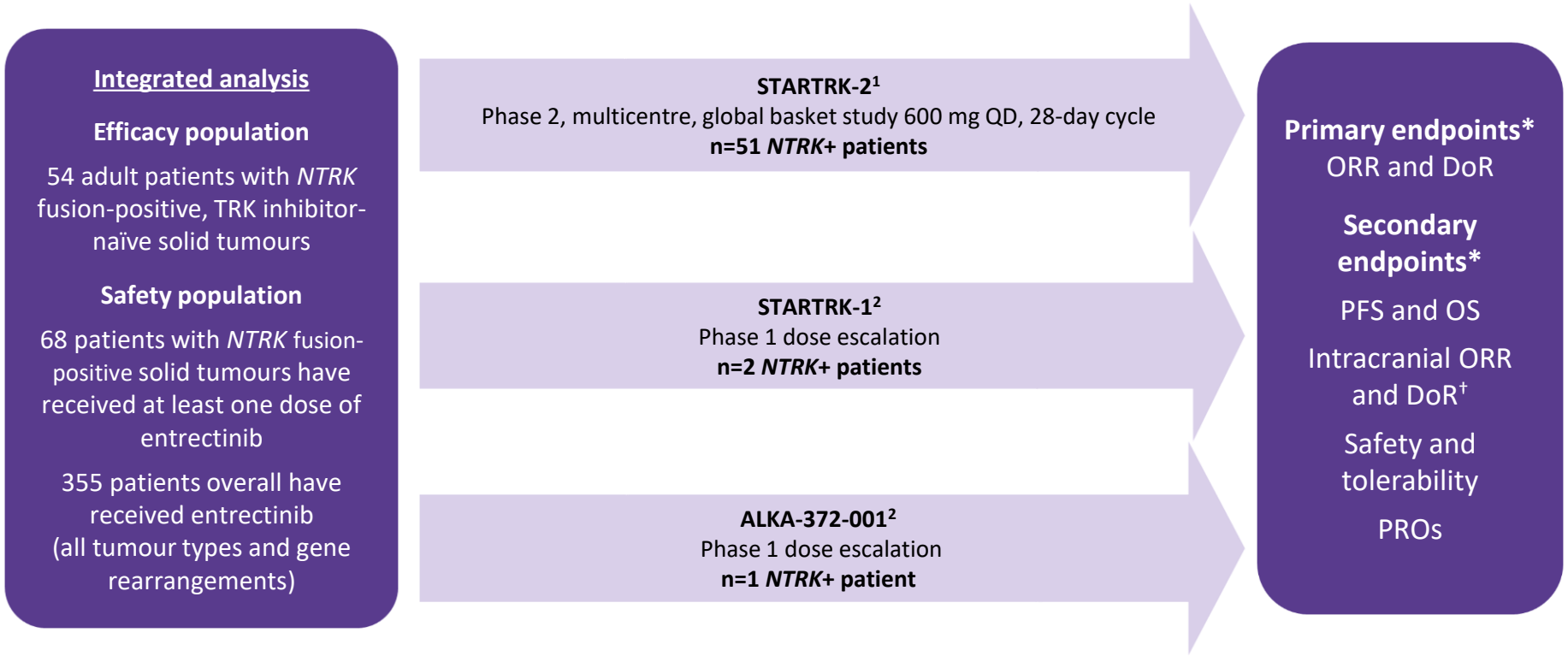
* Intracranial target tumour responses in patients with measurable disease, based on RECIST 1.1 sum of longest diameter. † Dose increased to 150 mg BID. ‡Progression in brain

BID, twice daily; NTRK, neurotrophic tyrosine receptor kinase; PR, partial response; RECIST, Response Evaluation Criteria In Solid tumours; SD, stable disease

Drilon A, et al. J Clin Oncol. 2019;37 no. 15_suppl:2006-2006

ENTRECTINIB

INTEGRATED EFFICACY AND SAFETY ANALYSIS OF ENTRECTINIB: STUDY DESIGN



Data cut-off: May 31, 2018

*BICR, blinded independent central review measured by RECIST v1.1

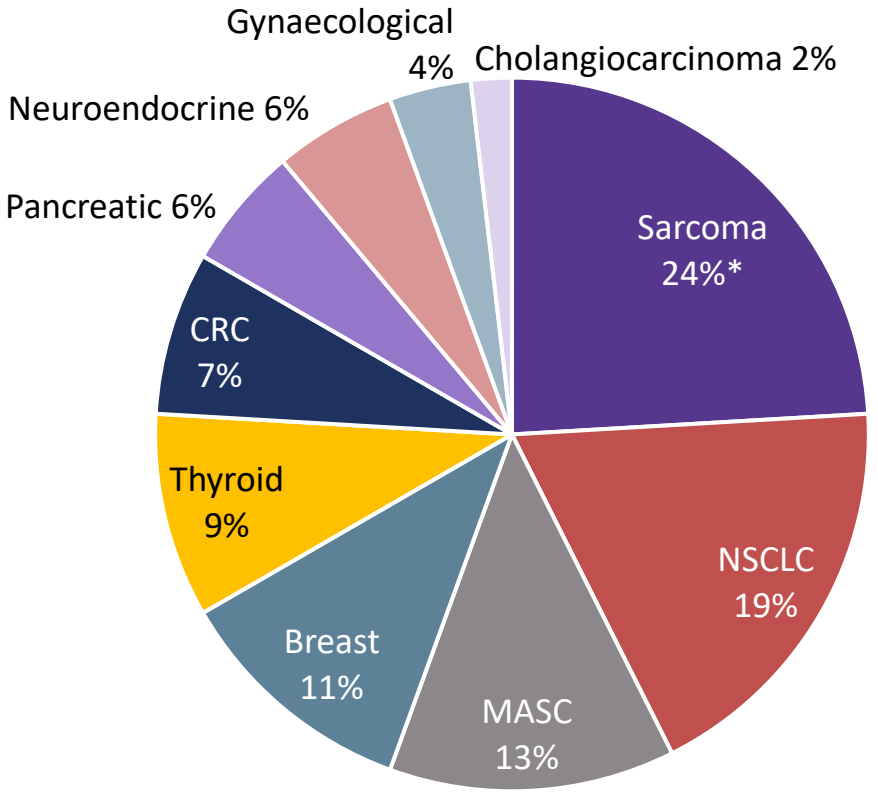
†Patients with measurable CNS lesions at baseline and patients with measurable and non-measurable CNS lesions at baseline

CNS, central nervous system; DoR, duration of response; NTRK, neurotrophic tyrosine receptor kinase; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PROs, patient-reported outcomes; QD, once daily; Response Evaluation Criteria In Solid tumours; TRK, tropomyosin receptor kinase

1. https://clinicaltrials.gov/ct2/show/NCT02568267
2. Drilon, et al. Cancer Discov 2017

INTEGRATED EFFICACY AND SAFETY ANALYSIS OF ENTRECTINIB: BASELINE CHARACTERISTICS

Baseline characteristics		*NTRK*+ tumour-agnostic population (n=54)
Age, years	Median (range)	57.5 (21-83)
Sex, %	Female Male	59.3 40.7
Race, %	White Asian	79.6 13.0
ECOG PS, %	0 1 2	42.6 46.3 11.1
Prior lines of systemic therapy, %	0 1 **≥2**	37.0 20.4 **42.6**
CNS disease at baseline, %		**22.2**



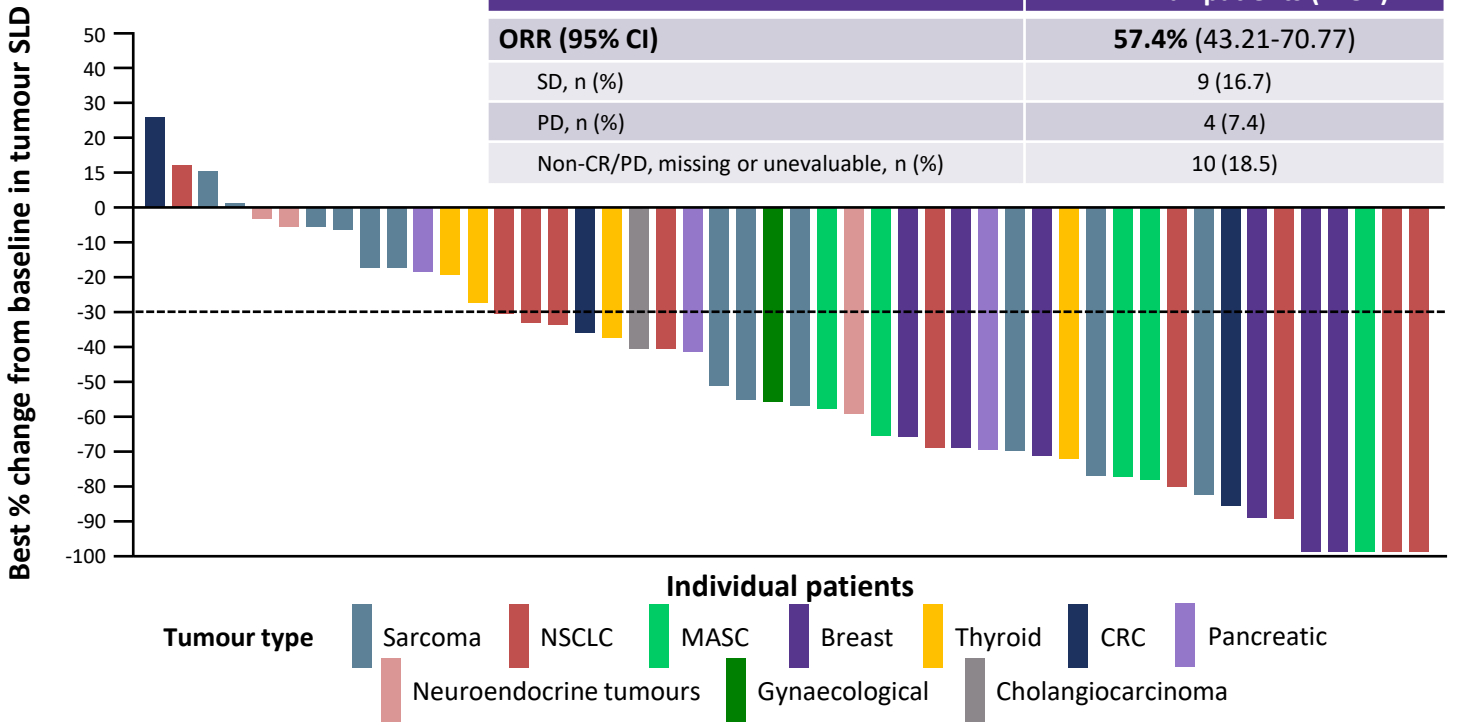
Data cut-off: May 31, 2018

* Does not include any paediatric congenital fibrosarcoma patients

CNS, central nervous system; CRC, colorectal cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; MASC, mammary analogue secretory carcinoma; NSCLC, nonsmall-cell lung carcinoma; NTRK, neurotrophic tyrosine receptor kinase

INTEGRATED EFFICACY AND SAFETY ANALYSIS OF ENTRECTINIB: INDIVIDUAL ORR BY TUMOUR TYPE* (BICR)

	NTRK+ all patients (n=54)
ORR (95% CI)	**57.4%** (43.21-70.77)
SD, n (%)	9 (16.7)
PD, n (%)	4 (7.4)
Non-CR/PD, missing or unevaluable, n (%)	10 (18.5)

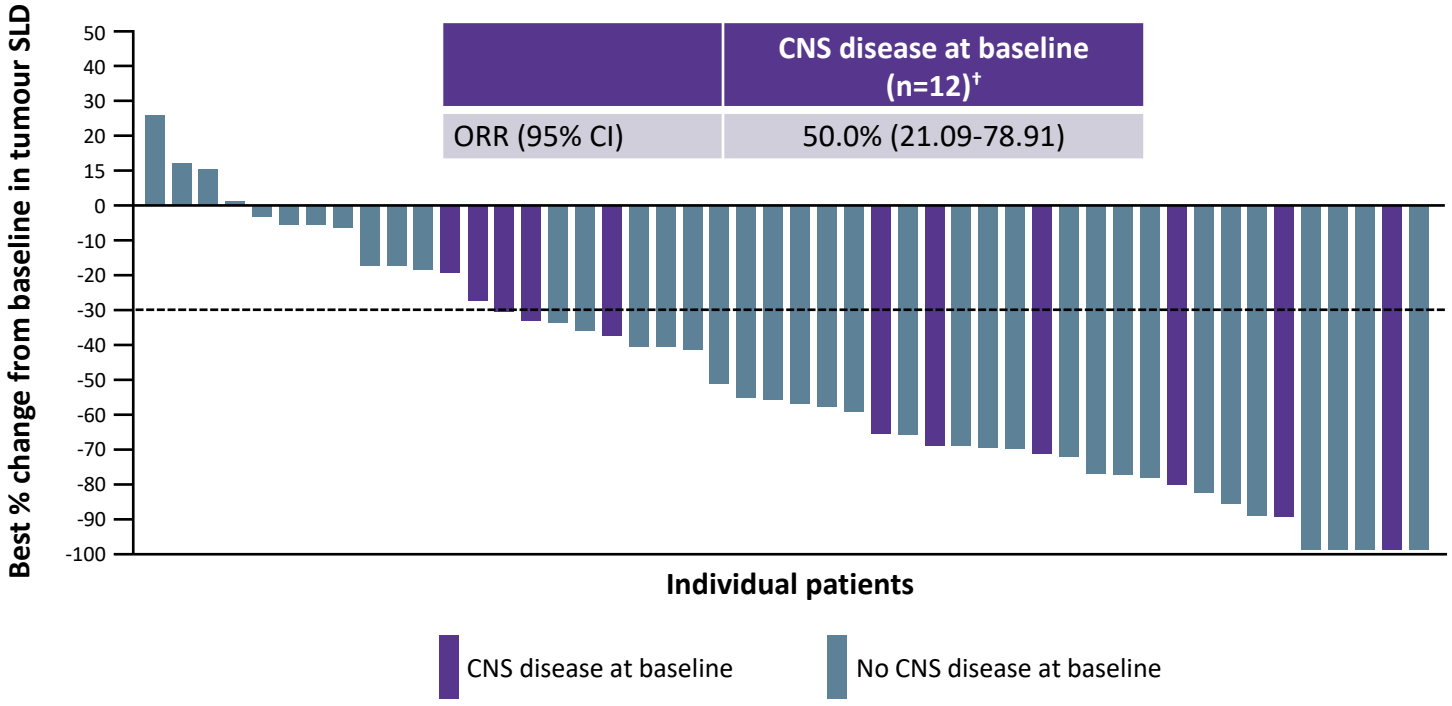


Data cut-off: May 31, 2018

* Patients with missing SLD percent change (n=6) were excluded from the plot

BICR, blinded independent central review; CI, confidence interval; CR, complete response; CRC, colorectal cancer; MASC, mammary analogue secretory carcinoma; NSCLC, nonsmall cell lung carcinoma; NTRK, neurotrophic tyrosine receptor kinase; ORR, overall response rate; PD, progressive disease; SD, stable disease; SLD, sum of longest diameter

INTEGRATED EFFICACY AND SAFETY ANALYSIS OF ENTRECTINIB: INDIVIDUAL ORR BY CNS TUMOUR INVOLVEMENT* (BICR)



Data cut-off: May 31, 2018

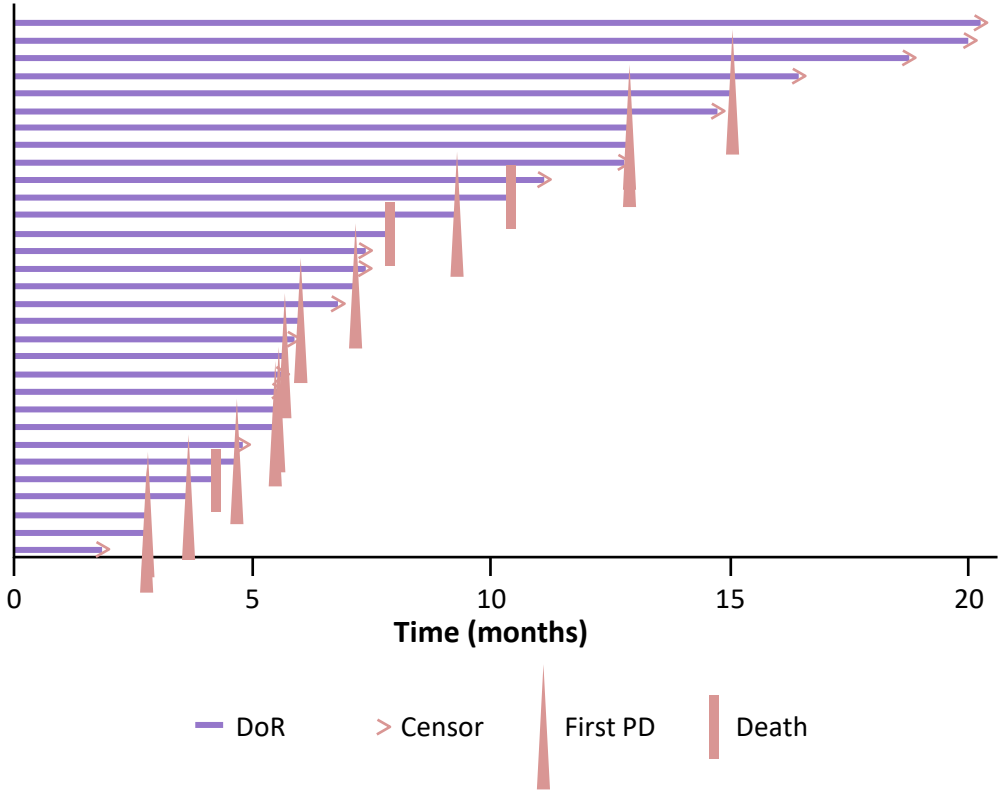
* Patients with missing SLD percent change (n=6) were excluded from the plot

† One of the 12 patients with CNS disease at baseline was excluded from the plot for having no post-baseline assessment

BICR, blinded independent central review; CNS, central nervous system; NTRK, neurotrophic tyrosine receptor kinase; ORR, overall response rate; SLD, sum of longest diameter

INTEGRATED EFFICACY AND SAFETY ANALYSIS OF ENTRECTINIB: DOR, PFS AND OS (BICR)

DoR with entrectinib (individual patients)



	DoR	PFS	OS
Patients included in analysis (responders, n)	31	54	54
Patients with event, n (%)	16 (51.6)	29 (53.7)	16 (29.6)
PD, n Death, n	13 3	20 9	– 16
Median time to event (months) 95% CI for median	**10.4** 7.1-NE	**11.2** 8.0-14.9	**20.9** 14.9-NE

Median follow up for survival (PFS, OS): 12.9 months

Median follow-up for DoR: 13.1 months

BICR, blinded independent central review; CI, confidence interval; DoR, duration of response; NE, not estimable; NTRK, neurotrophic tyrosine receptor kinase; OS, overall survival; PD, progressive disease; PFS, progression-free survival

INTEGRATED EFFICACY AND SAFETY ANALYSIS OF ENTRECTINIB: INTRACRANIAL ORR IN PATIENTS WITH CNS DISEASE AT BASELINE (BICR)

	CNS metastases at baseline by BICR (n=11)
Intracranial ORR, n(%) (95% CI)	6 (54.5) (23.38-83.25)
CR, n (%)	3 (27.3)
PR, n (%)	3 (27.3)
SD, n (%)	1 (9.1)
PD, n (%)	1 (9.1)
Non CR/PD, n (%)	2 (18.2)
Missing or unevaluable, n (%)	1 (9.1)
Intracranial median DoR, months (95% CI)	NE (5.0-NE)
Intracranial median PFS, months (95% CI)	14.3 (5.1-NE)

RECIST v1.1, data cut-off: May 31, 2018

BICR, blinded independent central review; CI, confidence interval; CNS, central nervous system; CR, complete response; DoR, duration of response; NE, not estimable; NTRK, neurotrophic tyrosine receptor kinase; ORR, overall response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria In Solid tumours; SD, stable disease

SUMMARY OF MAIN CLINICAL DATA: LAROTRECTINIB VS ENTRECTINIB

	larotrectinib[1]	entrectinib[2]
Target	Selective for *NTRK*	Multikinase
Response Rate (RR)	78%	57.4%
RR in CNS	71%	54.5%
Median PFS	36.8 months	11.2 months
Median OS	NE (95%CI 44.1-NE)	20.9 months
Adverse Events (AEs)	Mostly grade 1-2	Mostly Grade 1-2
Most common AEs	Fatigue (33%)	Dysguesia (47.1%)

[1]Data cut-off: 15 July 2019; [2]Data cut-off: 31 May 2018
CNS, central nervous system; NE, not estimable; NTRK, neurotrophic tyrosine receptor kinase; OS, overall survival; PFS, progression-free survival
[1]McDermott R, et al. Ann Oncol. 2020;31 (suppl_4):S1034-S1051

FINAL THOUGHTS

- Fusions are truly oncogenic drivers
- TRK inhibitors are truly transformative molecules
- The prevalence of *NTRK* fusion cancer patients is rare but treatment can be life-saving-TEST! TEST! TEST!

NTRK, neurotrophic tyrosine receptor kinase; TRK, tropomyosin receptor kinase

TESTING METHODOLOGIES AND TUMOUR-SPECIFIC ALGORITHMS

Prof. Frédérique Penault-Llorca
University of Clermont-Ferrand, France

DISCLOSURES

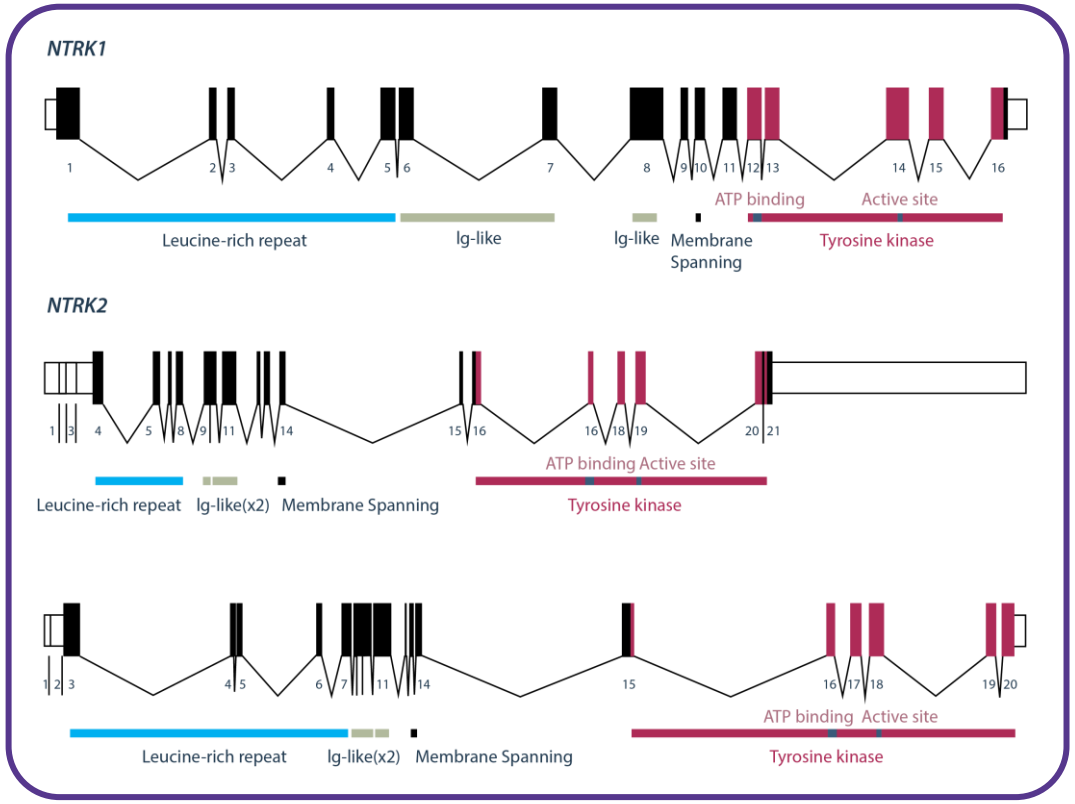
Research/Grant Funding: Abbvie, Astrazeneca, Bayer, BMS, MSD, Roche

Speaker fee: Abbvie, Agendia, AstraZeneca, Bayer, BMS, Chugai-Roche, Daiichi Sankyo, Eisai, Genomic Health, Illumina, Ipsen, Lilly, MSD, Myriad Genetics, Nanostring, Novartis, Pfizer, Pierre Fabre, Puma, Sanofi, Ventana-Roche.

NTRK GENE FUSION CHARACTERISTICS TO CONSIDER FOR DETECTION[1-5]

- *NTRK* gene fusions have **multiple fusion partners** and with **inconsistent** break points that are **tumour-agnostic**
- The resulting chimeric genes have a variable number of **intronic** regions with variable lengths
- The resulting chimeric genes have low complexity, **GC-rich sequences**
- TRK fusion proteins are **endogenously** expressed in some tumour/tissue types

➔ **Impact on testing strategies**



Source: Farago AF, et al. JCO Precis Oncol. 2018. 2018:PO.18.00037

ATP, adenosine triphosphate; Ig, immunoglobulin; NTRK, neurotrophic tyrosine kinase; TRK, tropomyosin receptor kinase

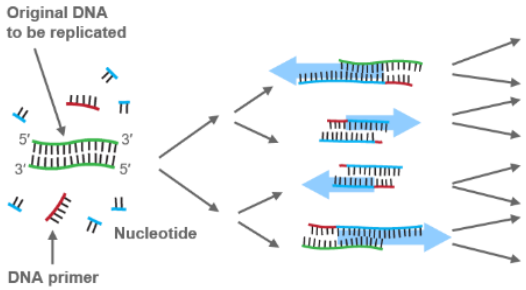
1. Vaishnavi A, et al. Cancer Discov. 2015;5:25-34; 2. Sigal D, et al. J Natl Compr Canc Netw. 2017;15:1317-22; 3. Gagan J and Van Allen EM. Genome Med. 2015;7:80; 4. Shaw AT, et al. Nat Rev Cancer. 2013;13:772-87; 5. Farago AF, et al. JCO Precis Oncol. 2018;2018:PO.18.00037

DIAGNOSTIC TESTING OVERVIEW

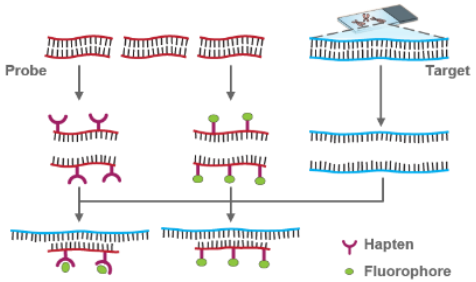
- *NTRK* gene fusions are oncogenic genomic alterations that are generally mutually exclusive with other driver gene mutations such as *ALK* and *BRAF*[1]
- Testing for *NTRK* gene fusions is essential to identify patients who harbour these genomic alterations and may therefore benefit from TRK inhibitors[1-3]

NTRK gene fusions can be detected indirectly or directly by multiple methods, including:[2-4]

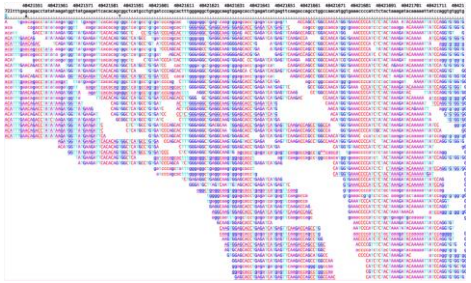
RT-PCR



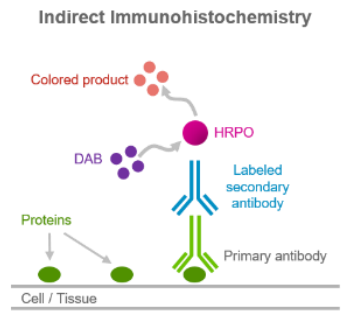
FISH



NGS



IHC*



*Only detects TRK protein expression, confirmatory genomic testing is required

ALK, anaplastic lymphoma kinase; BRAF, serine/threonine-kinase B-Raf/proto-oncogene B-Raf; FISH, fluorescence *in situ* hybridisation; IHC, immunohistochemistry; NGS, next generation sequencing; NTRK, neurotrophic tyrosine kinase; RT-PCR, reverse transcriptase-polymerase chain reaction; TRK, tropomyosin receptor kinase

1. Stransky N, et al. Nat Commun. 2014;5:4846; 2. Prasad ML, et al. Cancer. 2016;122:1097-1107; 3. Brenca M, et al. J Pathol. 2016;238:543-9;
4. Hechtman JF, et al. Am J Surg Pathol. 2017;41:1547-51

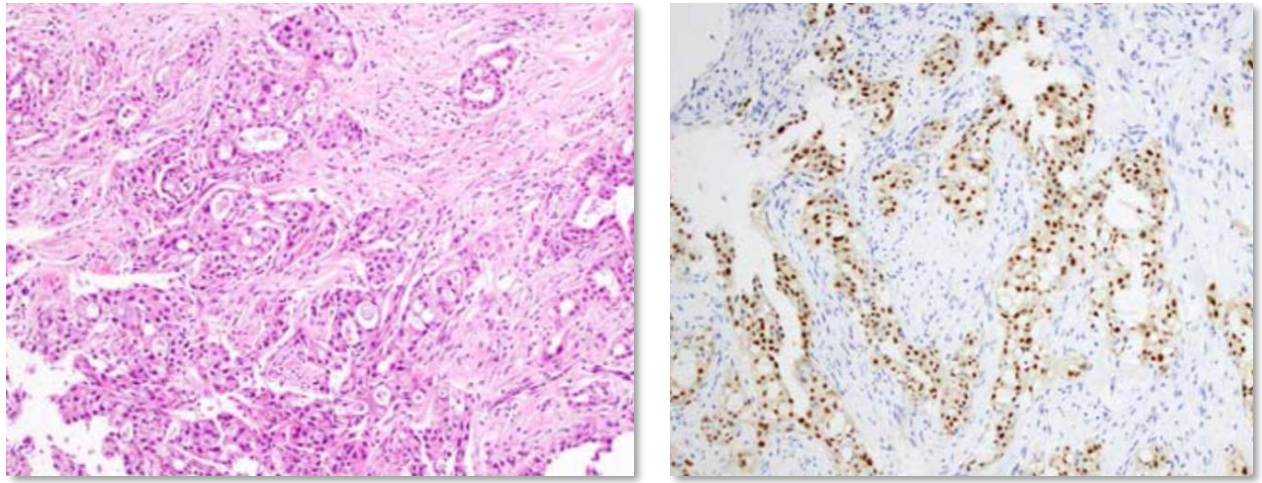
IMMUNOHISTOCHEMISTRY (IHC)

IMMUNOHISTOCHEMISTRY

NTRK connect®
POWERED BY COR2ED

THE PATTERN OF TRK EXPRESSION DETECTED BY IHC CAN BE VARIABLE IN INTENSITY AND SUBCELLULAR LOCALISATION

- **Nuclear** pan-TRK IHC can be considered a diagnostic surrogate of *NTRK3* fusions but other patterns can be associated
- Moderate to strong diffuse **cytoplasmic** pan-TRK IHC staining are more frequent in case of *NTRK1/NTRK2* fusions



ETV6-NTRK3 fusion positive case

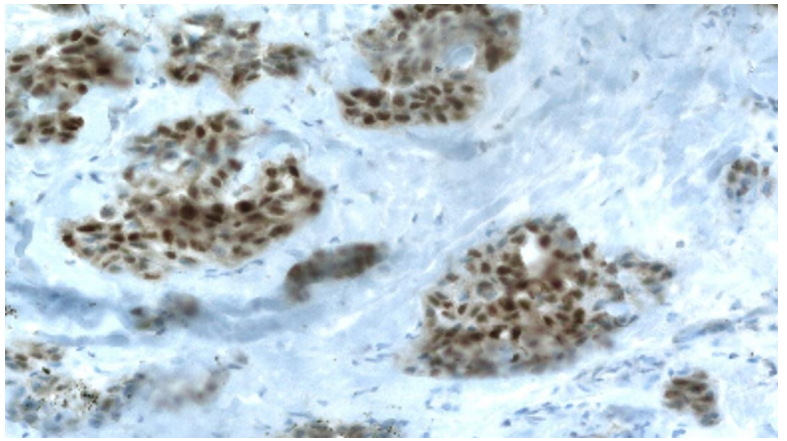
IHC, immunohistochemistry; NTRK, neurotrophic tyrosine kinase; TRK, tropomyosin receptor kinase

Images from Hechtman JF, et al. Am J Surg Pathol. 2017;41:1547-51

IMMUNOHISTOCHEMISTRY

Advantages

- Less expensive, reimbursed in many countries
- Fast turnaround time
- Protein localisation provides clues on the presence of specific fusions



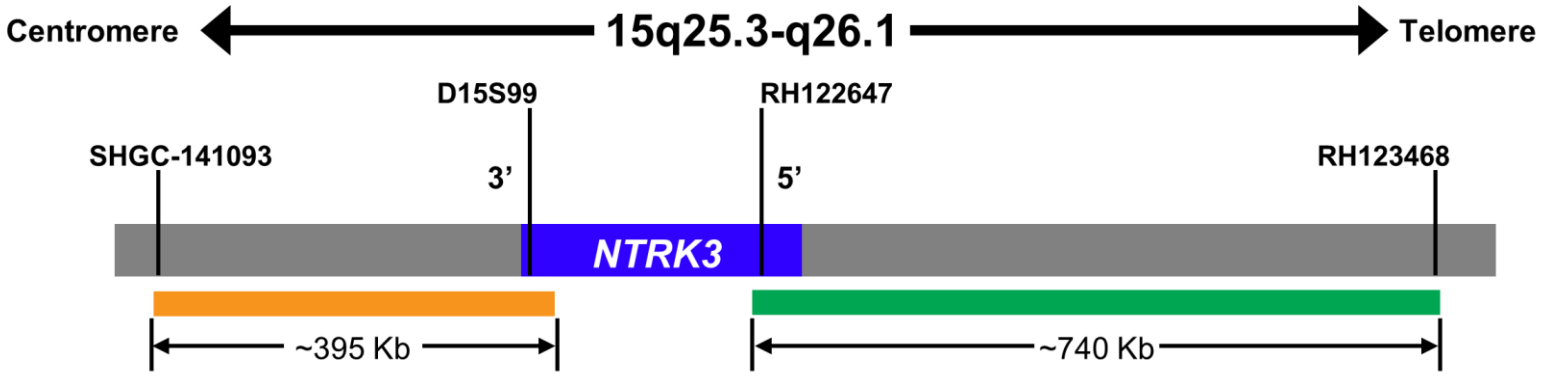
Disadvantages

- Low expression or rare types of fusion may give false negative results (low protein expression levels)
- Constitutive expression or low expression not associated with fusion (low specificity in nervous, neuroendocrine tumours), heterogeneous non specific staining in some sarcoma
- Does not detect involved genes and exons
- Does not detect concomitant alterations

FLUORESCENCE *IN SITU* HYBRIDISATION (FISH)

BREAK-APART FISH IS PARTICULARLY USEFUL FOR DETECTING GENE TRANSLOCATIONS

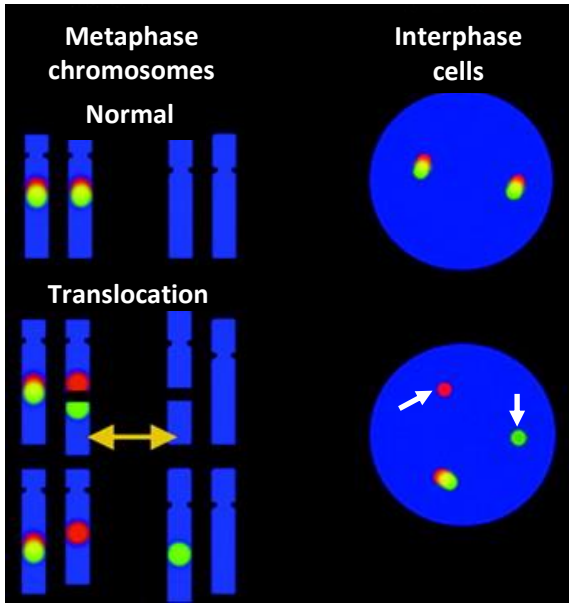
- Break-apart FISH uses separate, locus-specific, and differently coloured probes for the 5′ and 3′ ends of the gene of interest[1]



Zytovision ZytoLight® *NTRK3* Dual Colour Break Apart Probe

While break-apart FISH can identify gene disruptions in DNA, it cannot confirm in-frame, functional fusions

Yellow (red/green) signals in normal interphase nuclei versus split red and green signals in cell carrying translocation[2]



FISH, fluorescence *in situ* hybridisation; NTRK, neurotrophic tyrosine kinase

Zytovision. https://www.zytovision.com/downloads_products/datasheets/z-2206-ce-ivd.pdf. Accessed December 22, 2020
1. Cheng L, et al. J Path Clin Res. 2017;3:73-99; 2. Ventura RA, et al. J Mol Diag. 2006;8:141-51

FLUORESCENCE *IN SITU* HYBRIDISATION (FISH)

NTRK connect®
POWERED BY COR2ED

Advantages

- Commonly used method for detecting gene fusions
- Fast turnaround time

Disadvantages

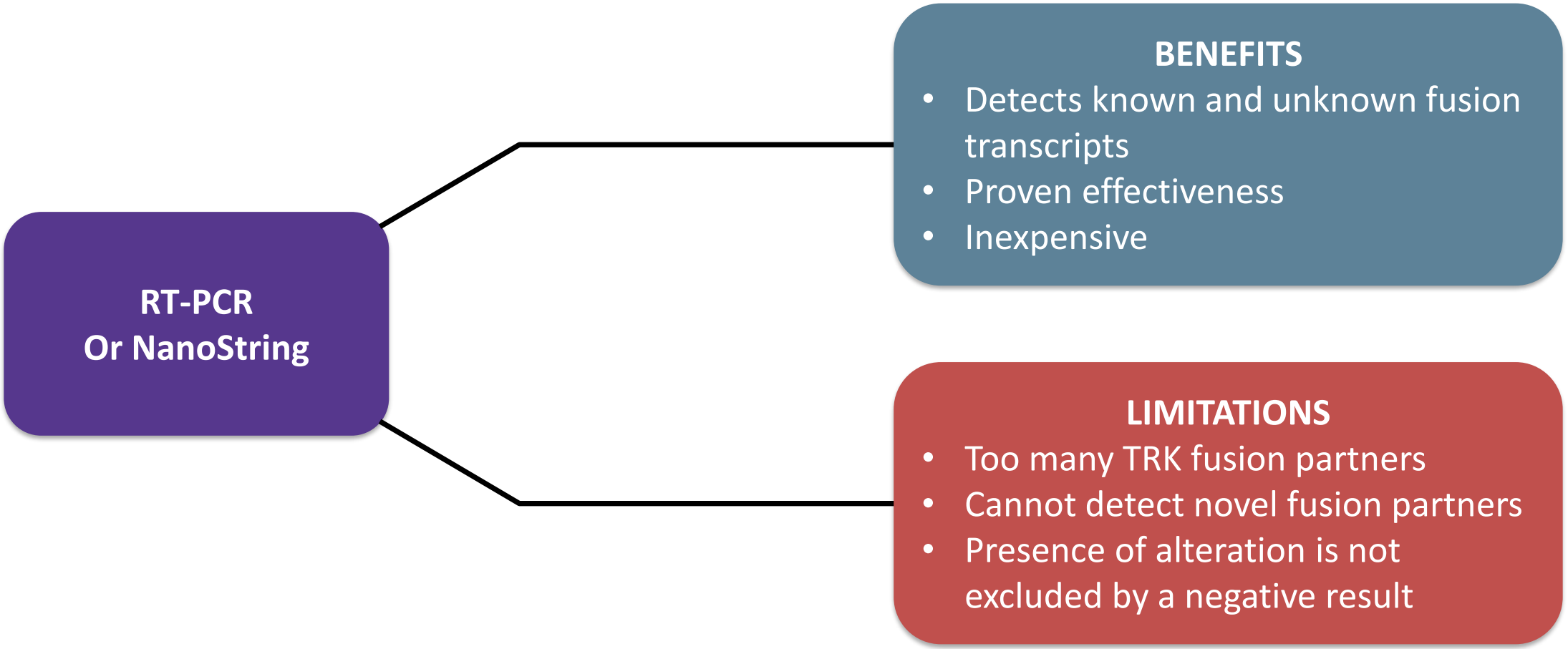
- Tests have to be run for each gene
- While break-apart FISH can identify gene disruptions in DNA, it cannot confirm in-frame, functional fusions
- No indication about the partner gene
- Subjective interpretation
- Requires specific equipment
- May show up to 30% false negative results

FISH, fluorescence *in situ* hybridisation

RT-PCR OR RNA TARGETED FUSION PANELS (NON NGS)

NGS, next generation sequencing; RT-PCR, reverse-transcriptase polymerase chain reaction

DETECTION OF FUSION TRANSCRIPTS BY RT-PCR

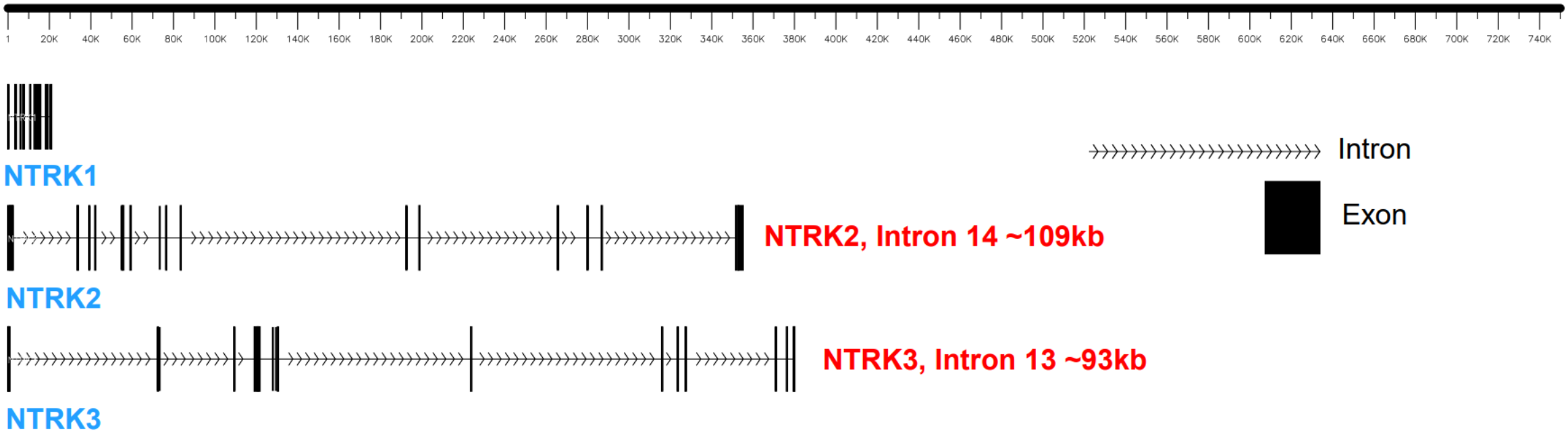


RT-PCR, reverse-transcriptase polymerase chain reaction; TRK, tropomyosin receptor kinase

NEXT GENERATION SEQUENCING (NGS)

THE CHALLENGE: DETECTING FUSIONS IN *NTRK1-3* GENES

- Because of large intronic spaces (and difficult regions within them), fusion detection by DNA NGS can be complicated
  - Lower capacity (fewer samples to multiplex to get appropriate coverage)
  - More complications with difficult introns



NTRK, neurotrophic tyrosine kinase; NGS, next generation sequencing

ADVANTAGES OF NGS IN DETECTING *NTRK* FUSIONS

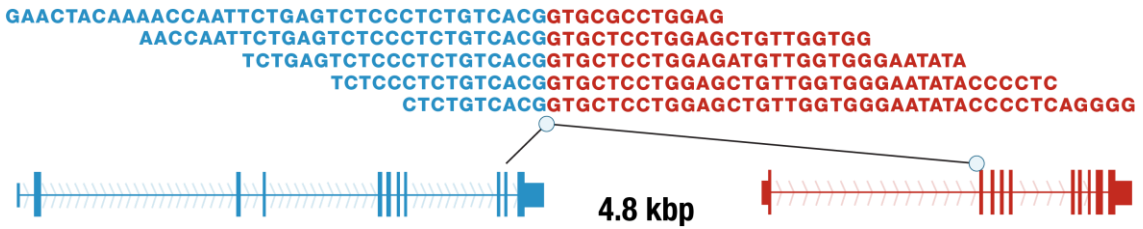
NTRK connect® POWERED BY COR2ED

General NGS

- High sensitivity and specificity potential
- Multiplexing: simultaneously queries multiple potentially actionable targets (e.g., *NTRK*, *ALK*, *ROS1*, *RET*)
- Detects both known and novel fusions, regardless of break point or fusion partner (depending on library preparation method)

RNA-based NGS

- Able to distinguish in-frame, transcribed gene fusions versus out-of-frame fusions
- Avoids difficulties of sequencing large intronic regions in the *NTRK* genes



RNA-based NGS is the preferred method for detecting *NTRK* fusions in cancer

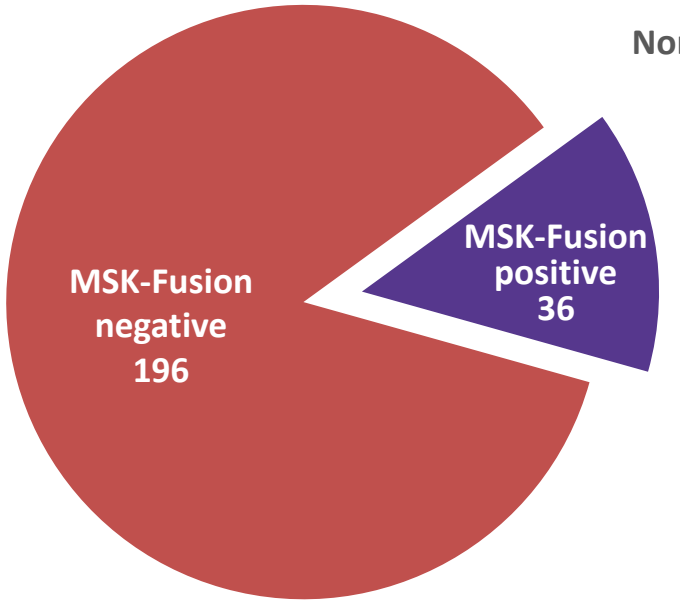
ALK, anaplastic lymphoma kinase; NGS, next generation sequencing; NTRK, neurotrophic tyrosine kinase

Kumar S, et al. Wiley Interdiscip Rev RNA. 2016;7:811-23

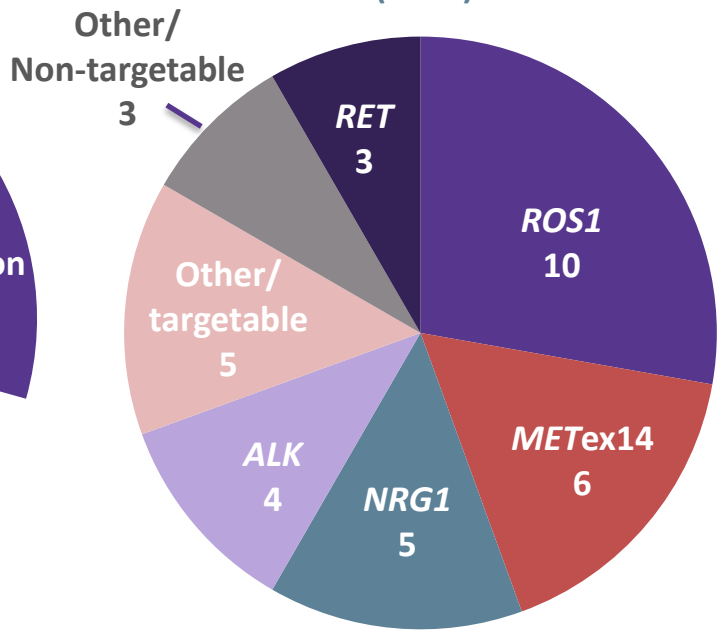
ADVANTAGES OF RNA NGS IN DETECTING *NTRK* FUSIONS

- Prospective DNA NGS MSK-IMPACT (Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets) of 2,522 lung adenocarcinomas
  - 195 (7.7%) fusions
  - 254 driver-negative ➔ 254 underwent RNASeq ➔ 27 in-frame fusions

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

* Response assessment by RECIST v1.1. ** Confirmed PR

ALK, anaplastic lymphoma kinase; NGS, next generation sequencing; NTRK, neurotrophic tyrosine kinase; PD, progressive disease; PR, partial response; SD, stable disease

Benayed R, et al. Clin Cancer Res. 2019;25:4712-22

CONCLUSION - DETECTING *NTRK* FUSIONS

NTRK connect® POWERED BY COR2ED

The perfect *NTRK* fusion test does not exist

	Pros	Cons	Comment
NGS	Comprehensive hypothesis free	Gene fusions require deliberate and challenging assay design	RNA > DNA for fusion sensitivity
RT-PCR	Proven, inexpensive	Too many TRK fusion partners	Only detects fusions you know to look for
FISH (break apart)	Built for fusions	Single-plex, fusion partner not identified	Three *NTRK* genes = six probes/colours
IHC	Proven, inexpensive	Single-plex, "positive" does not necessarily indicate fusion	*ALK* gene fusion success story

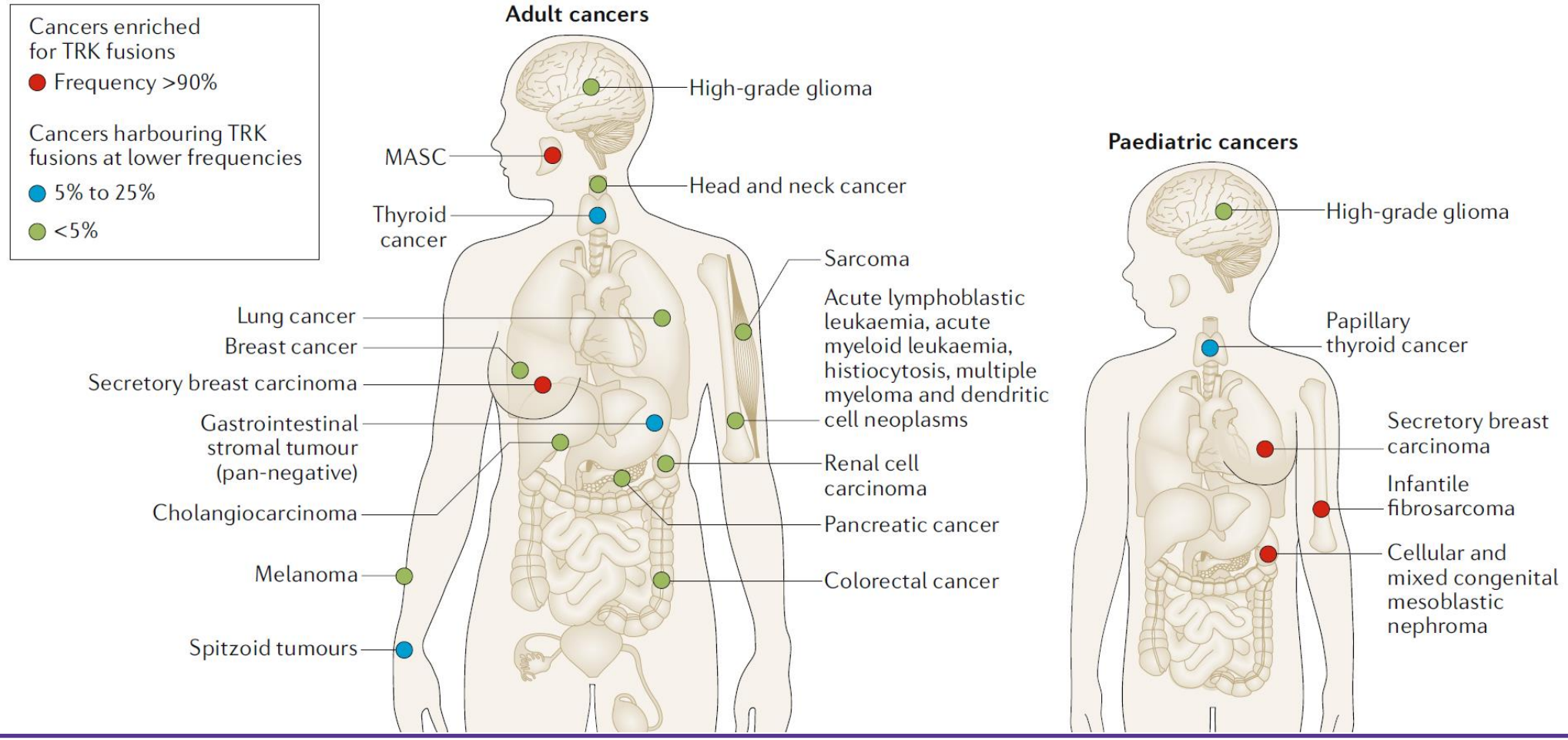
- All in one solution but not available everywhere and expensive
- Targeted research but simple tools
- Useful for the "pathognomonic" *NTRK* positive cancers
- Useful screening tool but low sensibility with some clones

ALK, anaplastic lymphoma kinase; FISH, fluorescence *in situ* hybridisation; IHC, immunohistochemistry; NGS, next generation sequencing; NTRK, neurotrophic tyrosine kinase; TRK, tropomyosin receptor kinase

https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM516803.pdf

TESTING STRATEGIES FOR *NTRK* FUSIONS

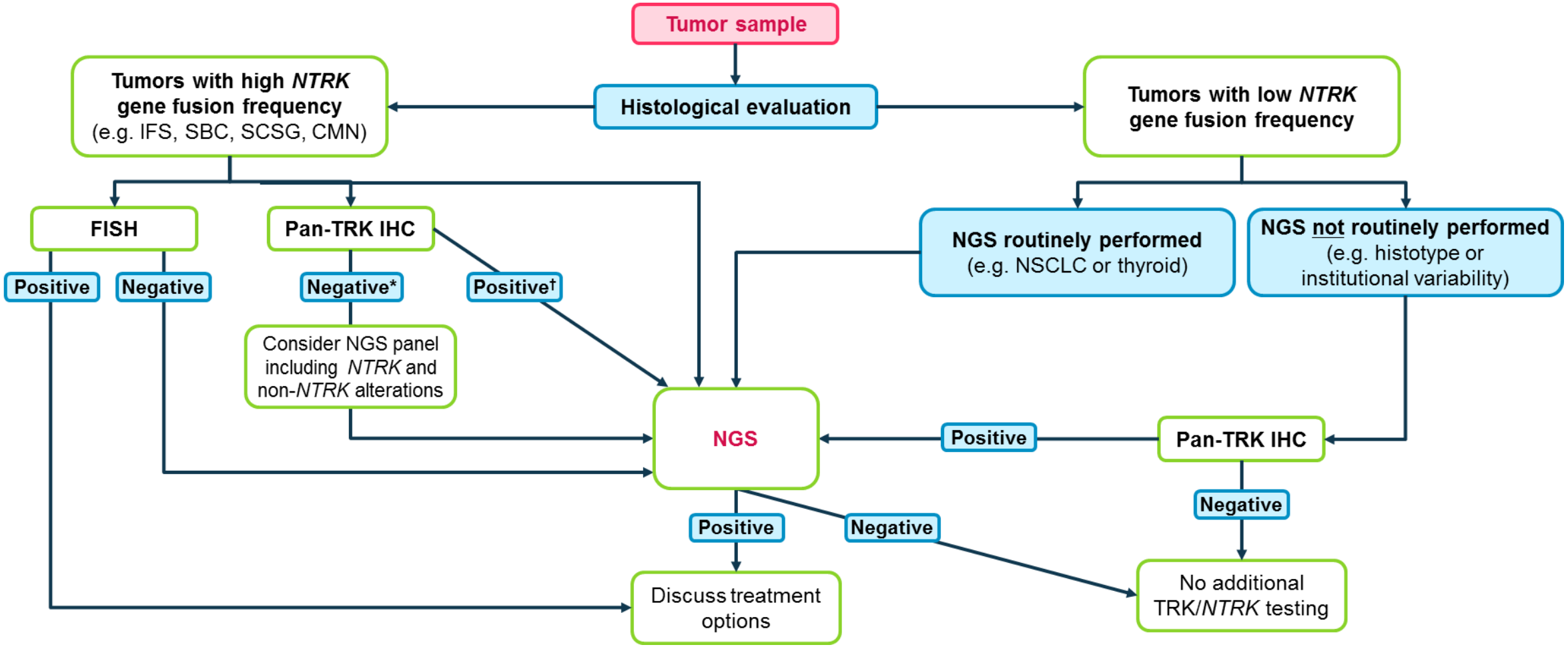
DISTRIBUTION AND FREQUENCY OF *NTRK* FUSIONS IN ADULT AND PAEDIATRIC TUMOURS



MASC, mammary analogue secretory carcinoma; NTRK, neurotrophic tyrosine kinase; TRK, tropomyosin receptor kinase

Cocco E, et al. Nature Rev Clin Oncol. 2018;15:731-47

TESTING ALGORITHM FOR *NTRK* FUSION CANCER



* If histology typical, then confirmation by NGS is recommended; † Concurrent NGS or FISH testing and treatment to be considered

CMN, congenital mesoblastic nephroma; FISH, fluorescence *in situ* hybridisation; IFS, infantile fibrosarcoma; ; IHC, immunohistochemistry; NGS, next generation sequencing; NSCLC, non-small-cell lung carcinoma; NTRK, neurotrophic tyrosine kinase; SBC, secretory breast carcinoma; SCSG, secretory carcinoma of the salivary glands; TRK, tropomyosin receptor kinase

Penault-Llorca F, et al. J Clin Pathol. 2019;72:460-7

TESTING GUIDANCE: IDEAL AND ALTERNATE TESTING BEHAVIOURS

NTRK connect® POWERED BY COR2ED

		Lung	Colorectal	Thyroid (RAI-refractory)	Sarcoma (GIST)
WHO **Who should I test?**	*Ideal*	Test all metastatic or locally advanced patients at diagnosis for oncogenic drivers (i.e. *EGFR, ALK, ROS1*) and *NTRK*	Test all metastatic or locally advanced patients at diagnosis along with other biomarkers, such as *KRAS, NRAS* and *BRAF*	Test all RAI-refractory patients for *NTRK*	Test all metastatic or locally advanced patients at diagnosis along with other biomarkers (*KIT, PDGFRA, SDH, NF1, BRAF, MDM/CDK4….*)
	Alternative	Negative for *EGFR, ALK, ROS1*, wild-type *BRAF* (Testing for *NTRK* should be conducted regardless of PD-L1 status)	**1) All MSI-H patients** 2) Wild-type *KRAS, NRAS* and *BRAF*	Negative *BRAF* V600	*KIT, PDGFRA*-negative …… patients
WHEN **When should I test?**	*Ideal*	At diagnosis of metastatic or locally advanced disease	At diagnosis of metastatic or locally advanced disease	At diagnosis of metastatic or locally advanced disease	At diagnosis of metastatic or locally advanced disease
	Alternative 1	At diagnosis after *EGFR, ALK, ROS1*	At metastatic diagnosis following *KRAS, NRAS, BRAF* and MSI	At metastatic diagnosis - following *BRAF*	At metastatic diagnosis following *KIT, PDGFRA*
	Alternative 2	After first- or second- line SOC	1) After first-line for MSI-H patients 2) Following first-line SOC for wild-type patients	After first-line SOC	After first- or second- line SOC
HOW **How should I test?**	*Ideal*	RNA-based NGS			
	Preferred	Pan-TRK IHC followed by molecular confirmation (except lung and CRC: NGS preferred if available)			
	Alternative	RT-PCR or FISH for *NTRK* 1,2,3			

ALK, anaplastic lymphoma kinase; BRAF, serine/threonine-kinase B-Raf/proto-oncogene B-Raf; CRC, colorectal cancer; EGFR, epidermal growth factor receptor; FISH, fluorescence *in situ* hybridisation; GIST, gastrointestinal stromal tumour; IHC, immunohistochemistry; MSI-H, microsatellite instability-high; NGS, next generation sequencing; NTRK, neurotrophic tyrosine kinase; PDGFRA, platelet-derived growth factor receptor alpha; PD-L1, programmed death-ligand 1; RAI, radioactive iodine; RT-PCR, reverse-transcriptase polymerase chain reaction; SOC, standard of care; TRK, tropomyosin receptor kinase

ROUTINE PAN-CANCER SCREENING: TUMOUR AGNOSTIC BIOMARKER

- **Screening for rare molecular events that occur across a variety of cancers can help to determine optimal treatment options for patients with advanced cancers**
  - NGS is broad and can detect many mutations, copy number variations, certain rearrangements, and microsatellite status
  - Mutation- and fusion-specific IHC have advantages in small samples or low tumour content cases
  - RNA testing can identify a variety of fusions in ‘driver-negative’ cancers

- **IHC with pan-TRK clones represent an interesting screening tools for frequent tumours (some limitations exist)**

IHC, immunohistochemistry; NGS, next generation sequencing; TRK, tropomyosin receptor kinase

ADVERSE EVENTS ASSOCIATED WITH TRK INHIBITORS

Prof. Ezra Cohen, MD, FRCPSC, FASCO
UC San Diego Health – Moores Cancer Center
La Jolla, California, USA

DISCLOSURES

Prof. Ezra Cohen has received honoraria from the following: ALX Oncology, Ascendis, Bayer, Bioline Rx, BMS, Debio, Dynavax, MSD, Merck , Regeneron and Sanofi.

BACKGROUND: LIST OF TRK INHIBITORS AND CURRENT DEVELOPMENT STAGE (ONGOING)

NTRK connect® POWERED BY COR2ED

TRK inhibitor	Targets	Development status in *NTRK*-positive population[1]
larotrectinib, LOXO-101	***NTRK1/2/3***	Approved*
entrectinib, RXDX-101	***NTRK1/2/3,*** *ALK, ROS1*	Approved**
selitrectinib, LOXO-195, BAY2731954	***NTRK1/3*** (resistant)	Phase 1/2, completed (NCT04275960) and recruiting (NCT03215511)
repotrectinib, TPX-0005	***NTRK1/2/3,*** *ALK, ROS1* (resistant) *JAK2, SRC, DDR1, FAK*	Phase 1/2, recruiting (NCT04094610; NCT03093116)
merestinib, LYS2801653	***NTRK1/2/3****, MET, MST1R, FLT3, AXL, MERTK, TEK, ROS1, DDR1/2; MKNK1/2*	Phase 2, active, not recruiting (NCT02920996)
sitravatinib, MGCD516	***NTRK1/2/3,*** *MET, KIT, PDGFRA, KDR, DDR2, RET, CBL*	Phase 1, active, not recruiting (NCT02219711)
taletrectinib, DS-6051b, AB-106	***NTRK1/2/3,*** *ROS1*	Phase 1/2, active, not recruiting (NCT02675491), not yet recruiting (NCT04617054)
cabozantinib, XL184	***NTRK1/2/3,*** *RET, ROS1, MET, and AXL*	Phase 2, recruiting (NCT01639508)
FCN-011	***NTRK1/2/3***	Phase 1, not yet recruiting (NCT04687423)

*Larotrectinib is approved in the US, Australia, Brazil, Canada, European Union, Hong-Kong, Israel, Saudi Arabia, Singapore, South Korea and Switzerland . **Entrectinib is approved in the US, Australia, European Union and Japan

ALK, anaplastic lymphoma kinase; CBL, casitas B-lineage lymphoma; DDR1/2, discoidin domain receptor tyrosine kinase 1/2; FAK, focal adhesion kinase; FLT3, FMS-like tyrosine kinase 3; JAK2, Janus kinase 2; KDR, kinase insert domain receptor; MKNK1/2, MAP kinase-interacting serine/threonine-protein kinase 1/2; MST1R, macrophage stimulating 1 receptor; NTRK, neurotrophic tyrosine receptor kinase; PDGFRA, platelet-derived growth factor receptor alpha; RET, rearranged during transfection; *ROS1*, c-ros oncogene 1; TRK, tropomyosin receptor kinase

1. Source : ClinicalTrials.gov website last accessed: on 11 January 2021

SAFETY PROFILE OF THE CURRENT APPROVED TRK INHIBITORS

larotrectinib (specific TRK inhibitor)
entrectinib (TRK, ROS1, ALK inhibitor)

ALK, anaplastic lymphoma kinase; *ROS1,* c-ros oncogene 1; TRK, tropomyosin receptor kinase

POOLED ANALYSIS OF AEs WITH LAROTRECTINIB

Data cutoff:
19 February 2019

Adult in Phase 1
Advanced solid tumours
NCT02122913
N=12

Paediatric in Phase 1/2
Advanced solid tumours
SCOUT: NCT02637687
N=50

Adult/adolescent in Phase 2
Advanced solid tumours
NAVIGATE: NCT02576431
N=97

	Treatment-emergent AEs, n (%)*			Treatment-related adverse events*	
	Grade 1-2	Grade 3	Grade 4	Grade 3	Grade 4
Fatigue	79 (30%)	6 (2%)	0	1 (<1%)	0
Alanine aminotransferase increased	64 (25%)	7 (3%)	2 (<1%)	7 (3%)	1 (<1%)
Cough	71 (27%)	1 (<1%)	0	0	0
Constipation	69 (27%)	1 (<1%)	0	0	0
Anaemia	44 (17%)	25 (10%)	0	6 (2%)	0
Aspartate aminotransferase increased	62 (24%)	6 (2%)	1 (<1%)	2 (<1%)	0
Dizziness	64 (25%)	2 (<1%)	0	1 (<1%)	0
Nausea	62 (24%)	2 (<1%)	0	2 (<1%)	0
Vomiting	62 (24%)	2 (<1%)	0	0	0
Diarrhoea	59 (23%)	3 (1%)	0	0	0
Pyrexia	50 (19%)	2 (<1%)	1 (<1%)	0	0
Dyspnoea	35 (13%)	6 (2%)	0	0	0
Myalgia	38 (15%)	3 (1%)	0	2 (<1%)	0
Peripheral oedema	40 (15%)	1 (<1%)	0	0	0
Headache	38 (15%)	1 (<1%)	0	1 (<1%)	0
Neutrophil count decreased	**18 (7%)**	**12 (5%)**	**2 (<1%)**	**4 (2%)**	**1 (<1%)**
Lymphocyte count decreased	22 (8%)	7 (3%)	2 (<1%)	2 (<1%)	0
Hypokalaemia	12 (5%)	8 (3%)	1 (<1%)	0	0
Hypophosphatemia	5 (2%)	9 (3%)	0	0	0

*Data are n (%). n=260. The adverse events listed here are those that occurred at any grade in at least 15% of patients, or at grade 3 or worse in at least 3% of patients, regardless of attribution. Refer to NTRK CONNECT for full publication details: https://ntrkconnect.info/ntrk-connect-key-publication-snapshot-1-larotrectinib-and-entrectinib-efficacy-and-safety-profile-in-solid-tumours/

AEs, adverse events
Source: Hong DS, et al. Lancet Oncol. 2020;21:531-40

EXPANDED POOLED ANALYSIS OF AEs WITH LAROTRECTINIB

NTRK connect® POWERED BY COR2ED

Expanded safety dataset (N=279)

Data cutoff:
15 July 2020

Adult in Phase 1
Advanced solid tumours
NCT02122913
N=13

Paediatric in Phase 1/2
Advanced solid tumours
SCOUT: NCT02637687
N=57

Adult/adolescent in Phase 2
Advanced solid tumours
NAVIGATE: NCT02576431
N=105

	Treatment-emergent AEs, n (%)			Treatment-related AEs, n (%)	
	Grade 1-2	Grade 3	Grade 4	Grade 3	Grade 4
Fatigue	85 (30%)	7 (3%)	0	1 (<1%)	0
Cough	82 (29%)	1 (<1%)	0	0	0
Alanine aminotransferase increased	70 (25%)	7 (3%)	2 (1%)	7 (3%)	2 (1%)
Constipation	75 (27%)	1 (<1%)	0	0	0
Diarrhoea	69 (25%)	4 (1%)	0	0	0
Dizziness	70 (25%)	3 (1%)	0	1 (<1%)	0
Anaemia	45 (16%)	26 (9%)	0	6 (2%)	0
Aspartate aminotransferase increased	64 (23%)	6 (2%)	1 (<1%)	2 (1%)	1 (<1%)
Vomiting	69 (25%)	2 (1%)	0	0	0
Nausea	67 (24%)	2 (1%)	0	2 (1%)	0
Pyrexia	60 (22%)	4 (1%)	1 (<1%)	0	0
Myalgia	45 (16%)	3 (1%)	0	2 (1%)	0
Dyspnoea	40 (14%)	7 (3%)	0	0	0
Arthralgia	43 (15%)	2 (1%)	0	1 (<1%)	0
Oedema peripheral	43 (15%)	1 (<1%)	0	0	0
Headache	41 (15%)	1 (<1%)	0	1 (<1%)	0
Weight increased	30 (11%)	10 (4%)	0	2 (1%)	0
Neutrophil count decreased	**18 (6%)**	**17 (6%)**	**2 (1%)**	**7 (3%)**	**1 (<1%)**
Lymphocyte count decreased	24 (9%)	10 (4%)	2 (1%)	3 (1%)	0

Data presented are from AEs in the expanded safety dataset (N=279)
The safety population included all patients enrolled in one of the three clinical trials, who received at least one dose of larotrectinib, regardless of TRK fusion status (n=279)
The AEs listed here are those that occurred at any grade in at least 15% of patients, or at Grade 3 or 4 in at least 3% of patients regardless of attribution
AEs, adverse events; TRK, tropomyosin receptor kinase
Source: McDermott R, et al. Ann Oncol. 2020;31 (suppl_4):S1034-S1051

INTEGRATED SAFETY DATA FOR ENTRECTINIB

Data cutoff:
31 May 2018

ALKA-372-001: Phase 1
Solid tumours
EudraCT 2012-000148-88
N=1

STARTRK-1: Phase 1/2
Solid tumours
NCT02097810
N=2

STARTRK-2: Phase 2
Solid tumours
NCT02568267
N=51

Treatment-related adverse events (n=68)*	Grade 1–2	Grade 3	Grade 4
Dysgeusia	32 (47%)	0	0
Constipation	19 (28%)	0	0
Fatigue	19 (28%)	5 (7%)	0
Diarrhoea	18 (27%)	1 (2%)	0
Oedema peripheral	16 (24%)	1 (2%)	0
Dizziness	16 (24%)	1 (2%)	0
Blood creatinine increased	12 (18%)	1 (2%)	0
Paraesthesia	11 (16%)	0	0
Nausea	10 (15%)	0	0
Vomiting	9 (13%)	0	0
Arthralgia	8 (12%)	0	0
Myalgia	8 (12%)	0	0
Weight increased	8 (12%)	7 (10%)	0
AST increased	**7 (10%)**	**0**	**1 (2%)**
ALT increased	**6 (9%)**	**0**	**1 (2%)**
Muscular weakness	6 (9%)	1 (2%)	0
Anaemia	5 (7%)	8 (12%)	0
Asthenia	5 (7%)	0	0
Peripheral sensory neuropathy	4 (6%)	1 (2%)	0
Neutrophil count decreased	4 (6%)	0	0
Rash	4 (6%)	0	0

Treatment-related adverse events (n=68)*	Grade 1–2	Grade 3	Grade 4
Disturbance in attention	3 (4%)	0	0
Pain of skin	3 (4%)	0	0
Neutropenia	3 (4%)	2 (3%)	0
Localised oedema	2 (3%)	1 (2%)	0
Hyperaesthesia	2 (3%)	0	0
Ataxia	2 (3%)	0	0
Platelet count decreased	2 (3%)	0	0
Hyperuricaemia	**2 (3%)**	**0**	**2 (3%)**
Hypophosphatemia	2 (3%)	2 (3%)	0
Dehydration	2 (3%)	0	0
Diplopia	1 (2%)	1 (2%)	0
Hypotension	1 (2%)	1 (2%)	0
Pyrexia	1 (2%)	0	0
Lymphocyte count decreased	1 (2%)	0	0
Pruritus	1 (2%)	0	0
Hypoxia	1 (2%)	0	0
Fall	1 (2%)	0	0
Osteoarthritis	0	1 (2%)	0
Blood uric acid increased	**0**	**0**	**1 (2%)**
Hypermagnesemia	0	1 (2%)	0
Cardiac failure	0	1 (2%)	0
Cardiac failure congestive	0	1 (2%)	0

*Data are n (%). n=68. The treatment-related adverse events listed here are those that occurred in the *NTRK* fusion-positive safety-evaluable population. Refer to NTRK CONNECT for full publication details: https://ntrkconnect.info/ntrk-connect-key-publication-snapshot-1-larotrectinib-and-entrectinib-efficacy-and-safety-profile-in-solid-tumours/

ALT, alanine aminotransferase; AST, aspartate aminotransferase; NTRK, neurotrophic tyrosine receptor kinase

Doebele RC, et al. Lancet Oncol. 2020;21:271-82

CHARACTERISATION OF ON-TARGET ADVERSE EVENTS CAUSED BY TRK INHIBITOR THERAPY

Liu D, et al. Ann Oncol. 2020;31:1207-15

TRK, tropomyosin receptor kinase

DEFINITION & RETROSPECTIVE STUDY DESIGN

- **On-target** refers to pronounced and adverse pharmacological effects at the target molecule of interest in the test system[1]
- **Off-target** refers to adverse effects as a result of modulation of other target molecules; these may be related biologically or totally unrelated to the target of interest[1]

Eligibility criteria

- Treated in the Early Drug Development Service of Memorial Sloan Kettering Cancer Center between January 1st 2013→ April 1st 2019
- Pathologic evidence of a solid tumour
- Advanced or unresectable disease
- treated with at least one dose of a tyrosine kinase inhibitor with potent anti-TRK activity

n= 96

Data collection

- Demographics
- Toxicity assessment
- AE management

Treatment-emergent AEs Analysis

AE likely to be mediated by TRK inhibition were analysed:

- Paraesthesias
- Weight gain
- Dizziness with or without ataxia
- Pain with temporary or permanent TRK inhibitor withdrawal

AE, adverse event; TRK, tropomyosin receptor kinase

1. DG Rudmann. Toxicol Pathol. 2013;41:310-4

DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Clinicopathologic features of the study population (n=96)	n (%) and continuous as median (range)
Age* (years)	52 (5-81)
Female sex	49 (51%)
Histology	
Lung	43 (45%)
Gastrointestinal	10 (10%)
Salivary	8 (8%)
Sarcoma	8 (8%)
Thyroid	6 (6%)
Melanoma	6 (6%)
Primary brain tumour	5 (5%)
Neuroblastoma	5 (5%)
Other	7 (7%)

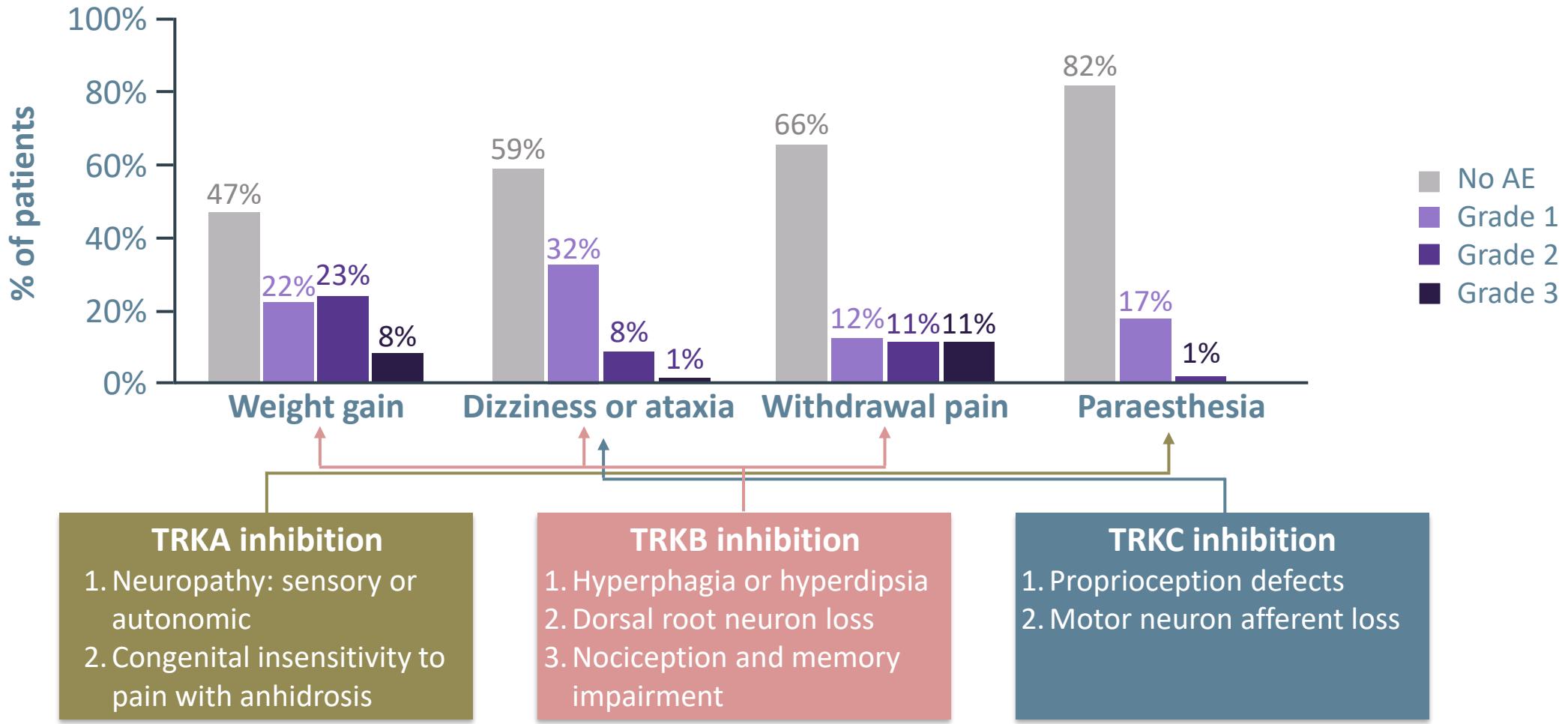
Clinicopathologic features of the study population (n=96)	n (%) and continuous as median (range)
Genomic alteration	
NTRK fusion	**39 (41%)**
ROS1 fusion	24 (25%)
Other**	29 (30%)
Unknown	4 (4%)
TRK inhibitor	
First-generation TKI	81 (84%)
Other TKI	30 (31%)
TRK inhibitor duration (months)	6 (1-42)

*Seven patients were <18 years old

**Other alterations included *NTRK* mutation (N = 1), *NTRK* amplification (N = 2), *ROS1* mutation (N = 1), and *ALK* fusion/mutation (N = 25)

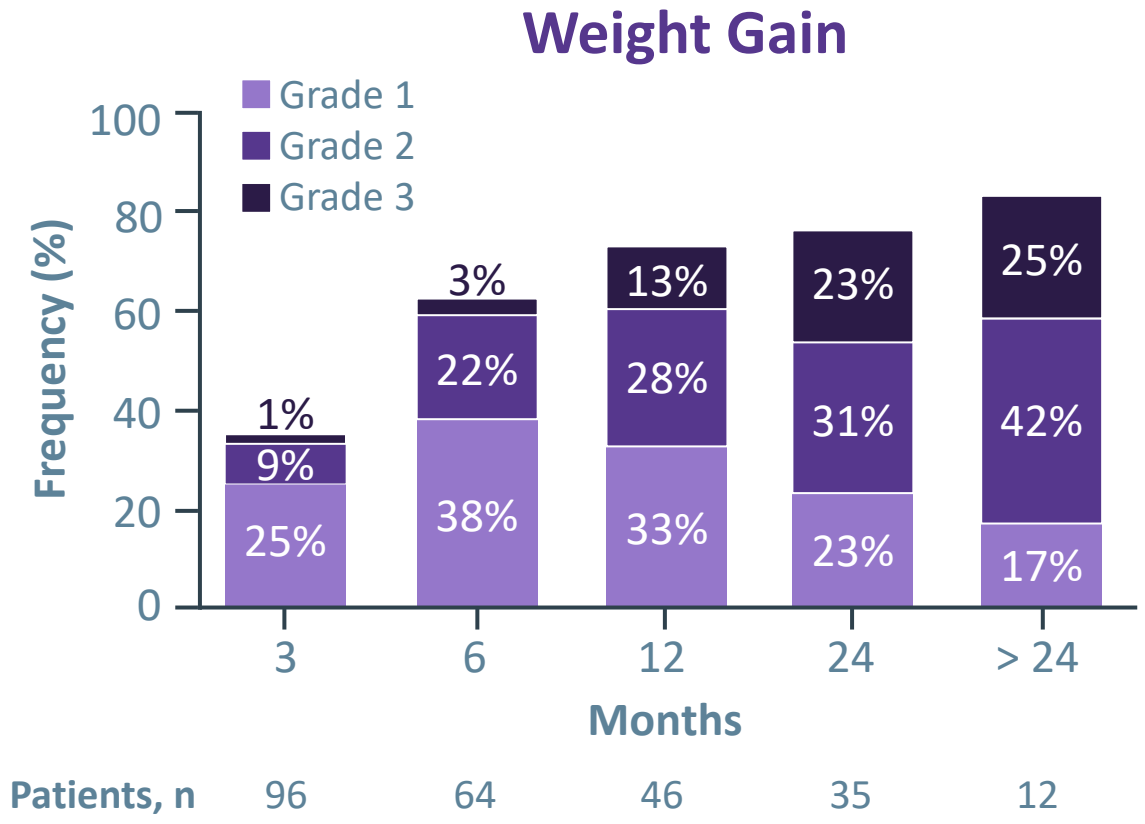
ALK, anaplastic lymphoma kinase; NTRK, neurotrophic tyrosine receptor kinase; *ROS1,* c-ros oncogene 1; TKI, tyrosine kinase inhibitor; TRK, tropomyosin receptor kinase

SAFETY PROFILE OF ON-TARGET AEs WITH TRK INHIBITION



AEs, adverse events; TRK A/B/C, tropomyosin receptor kinase A/B/C

WEIGHT GAIN MANAGEMENT



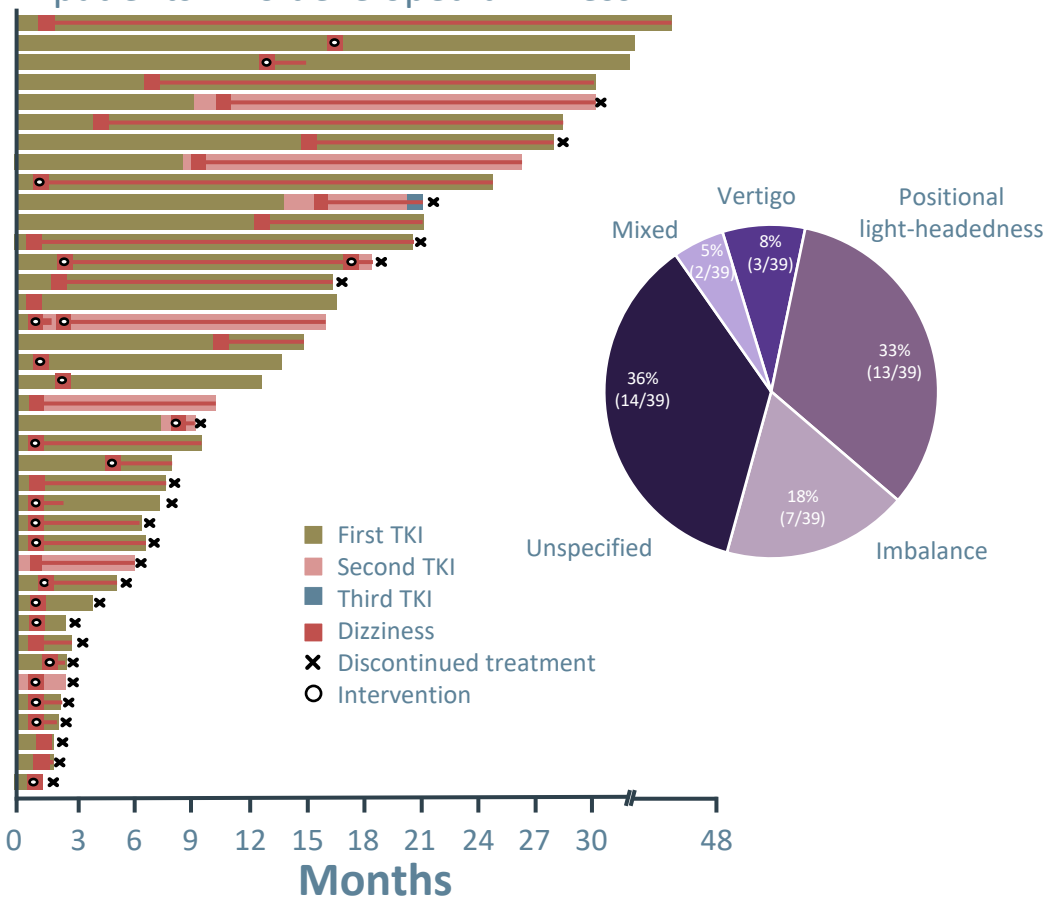
Supportive medication in weight gain	
Agent(s)	**Mechanism of action**
Liraglutide	GLP-1 analogue
Orlistat	Inhibits fat absorption
Phentermine/ topiramate combination	Increases norepinephrine release; GABA receptor agonist
Lorcaserin	5-HT_{2C} receptor agonist
Naltrexone/ bupropion combination	μ-opioid receptor antagonist; dopamine and norepinephrine reuptake inhibitor
Metformin	Modulates hypothalamic appetite regulatory centers

➔Authors recommend to monitor serially weight gain during treatment with TRK Inhibitor

5-HT, 5-hydroxytryptamine; GABA, γ-aminobutyric acid; GLP-1, glucagon-like peptide-1; TRK, tropomyosin receptor kinase

DIZZINESS MANAGEMENT

Time to treatment discontinuation in patients who developed dizziness*



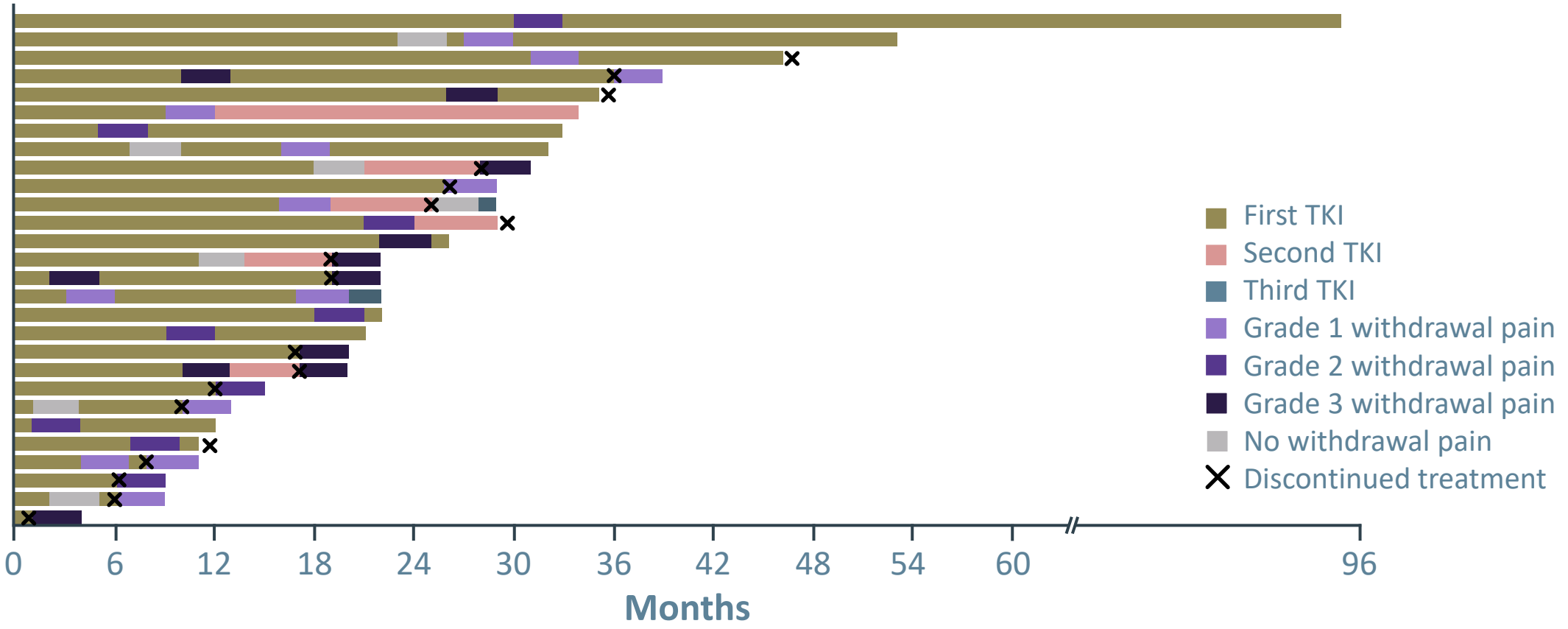
Supportive medication in dizziness management		
	Agent(s)	**Mechanism of action**
Dizziness (ataxia or vertigo)	Meclizine	H_1 histamine receptor antagonist, suppresses vestibular stimulation, anticholinergic
	Scopolamine	Antagonises histamine and serotonin
Dizziness (orthostasis)	Midodrine	α_1 adrenergic receptor agonist, increases vascular tone
	Fludrocortisone	Mineralocorticoid
	Droxidopa	Metabolized to norepinephrine, induces vasoconstriction

➔ Authors recommend to characterise the dizziness and to manage it accordingly

*Each bar represents a single patient. Pie chart shows the frequency distribution of the categories of dizziness that patients experienced.
TKI, tyrosine kinase inhibitor

WITHDRAWAL PAIN MANAGEMENT

Time to discontinuation discontinuation in patients who developed withdrawal pain*



➔ Authors highlight that withdrawal pain can occur with temporary or permanent TKI treatment with anti-TRK activity discontinuation

*Each bar represents a single patient
TKI, tyrosine kinase inhibitor; TRK, tropomyosin receptor kinase

CONCLUSION

- Identifying AEs related to TRK inhibitors are important in order to manage them during treatment approaches
- **On-target AEs with TRK inhibition can occur** as shown in the retrospective study analysing patients with advanced or unresectable solid tumours treated with at least one dose of a TKI with potent anti-TRK activity
- **Dizziness, weight gain and withdrawal pain are the three identified on-target AEs**
- **On-target AE profile is consistent with the known physiological mechanism of the TRK signalling pathway**

- **Limitations:**
  - The inhibitory actions of TKIs **are not only specific to TRKs**
  - In the retrospective study, **only 41% harboured an *NTRK*-positive solid tumour**
- **Due to the small size of the study, more detailed assessment of no-target AEs is needed, especially with the TRK-specific inhibitors such as larotrectinib**

AE, adverse event; NTRK, neurotrophic tyrosine receptor kinase; TKI, tyrosine kinase inhibitor; TRK, tropomyosin receptor kinase

TREATING *NTRK* FUSION CANCERS TOMORROW-NEXT STEPS?

David S. Hong, MD

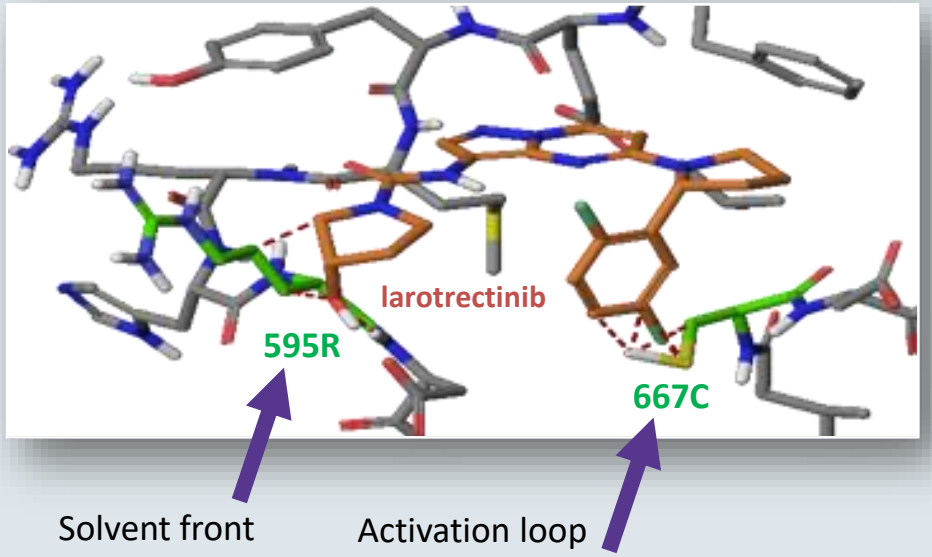
The University of Texas MD Anderson Cancer Center.
Professor
Deputy Chairman in the Dept of Investigational Cancer Therapeutics
(Phase 1 Program)
Associate Vice President of Clinical Research

RESISTANCE MECHANISMS

MECHANISM OF RESISTANCE TO FIRST GENERATION OF TRK INHIBITORS

- Mutations that limit drug binding are the most common form of acquired resistance; often, the oncogene-addicted tumour remains addicted to the same oncogene
- Early lines of evidence offer a molecular understanding of potential mechanisms of resistance to larotrectinib in patients with NTRK gene fusions:
  - Preclinical modelling
  - Precedent paralogous targets (e.g. ALK, ROS1)
  - Clinical case reports[1,2]

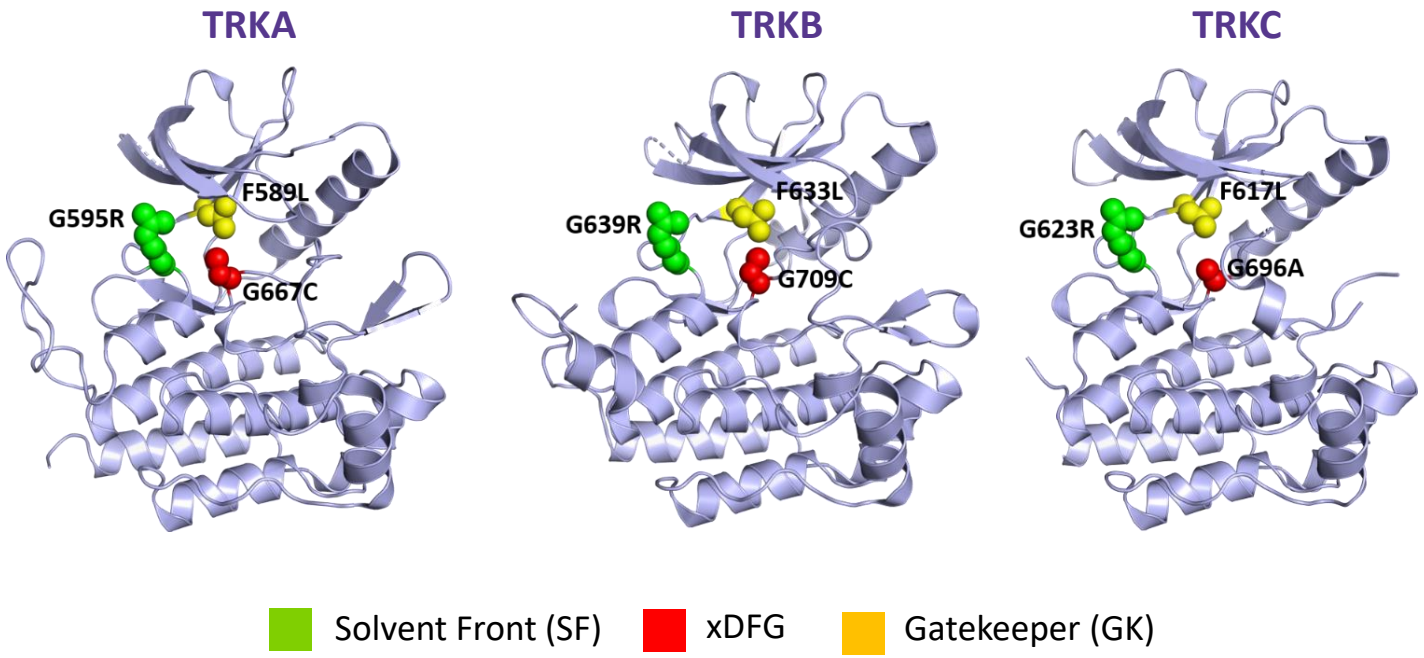
larotrectinib bound to ATP-binding pocket of TRKA: steric hindrance caused by G595R or G667C



ALK, anaplastic lymphoma kinase; ATP, adenosine triphosphate; NTRK, neurotrophic tyrosine receptor kinase; ROS1, proto-oncogene tyrosine-protein 1; TRK, tropomyosin receptor kinase

1. Russo M, et al. Cancer Discov. 2016;6:36-44; 2. Drilon A, et al. Ann Oncol. 2016;27:920-6

ON-TARGET RESISTANCE TO TRK INHIBITORS

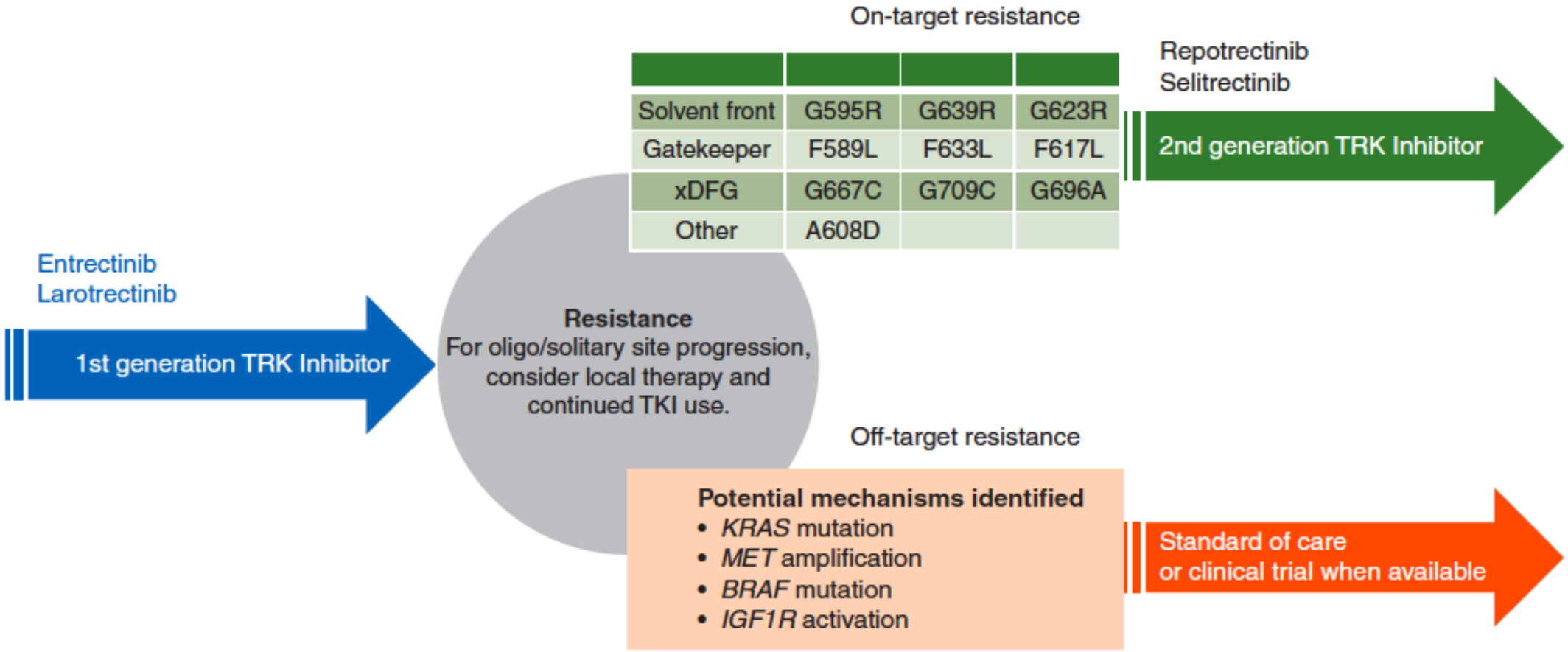


Acquired TRK kinase domain mutations in three recurrent motifs result in on-target resistance to current generation of inhibitors

TRK, tropomyosin receptor kinase; xDFG, xDFG motif

Cocco E, et al. Nat Rev Clin Oncol. 2018;15:731-47

ON-TARGET AND OFF-TARGET RESISTANCE TO TRK INHIBITORS



BRAF, v-raf murine sarcoma viral oncogene homolog B1; IGF1R, insulin-like growth factor 1 receptor; MET, c-MET proto-oncogene; KRAS, Ki-ras2 Kirsten rat sarcoma viral oncogene homolog; TKI, tyrosine kinase inhibitor; TRK, tropomyosin receptor kinase; xDFG, xDFG motif

Drilon A., Ann Oncol. 2019;30(Suppl_8):viii23-viii30

NEXT-GENERATION TRK INHIBITORS

TRK, tropomyosin receptor kinase

MAIN NEXT-GENERATION TRK INHIBITORS AND CLINICAL DEVELOPMENT STATUS

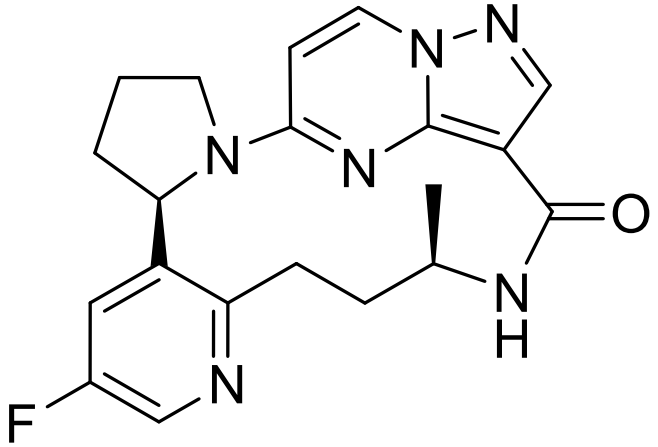
NTRK connect®
POWERED BY COR2ED

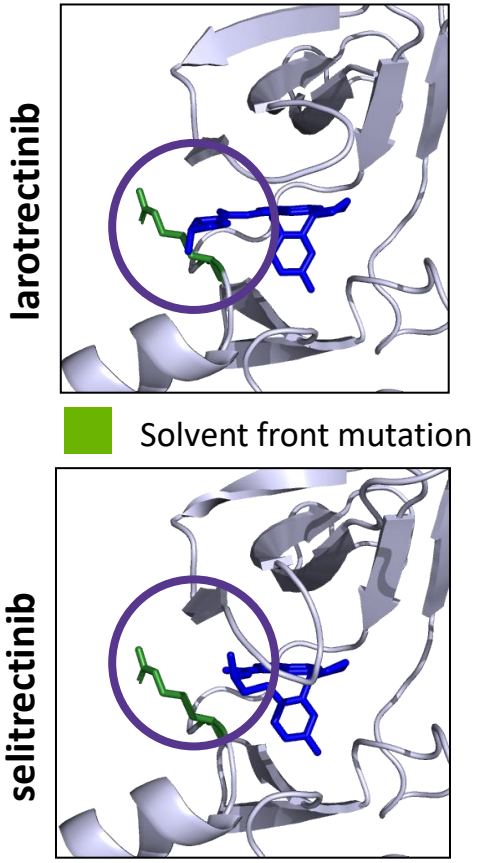
Drug Name (Sponsor)	Molecular Targets	Development Stage and tumour Types
selitrectinib, LOXO-195, BAY2731954 (Bayer)	***NTRK1/3*** (solvent front, XDFG, gatekeeper mutations)	Phase 1/2, recruiting (NCT04275960; NCT03215511)
repotrectinib, TPX-0005 (Turning Point)	***NTRK1/2/3*** (solvent front, XDFG, gatekeeper mutations), *ALK, ROS*	Phase 1/2, recruiting (NCT04094610; NCT03093116)

ALK, anaplastic lymphoma kinase; NTRK, neurotrophic tyrosine receptor kinase; ROS, proto-oncogene tyrosine-protein; TRK, tropomyosin receptor kinase; xDFG, xDFG motif

SELITRECTINIB (LOXO-195/BAY 2731954)

- Potent second-generation inhibitor of all three TRK tyrosine kinases with IC_{50} between 2.0 and 9.2 nM for the 3 on-target resistance mutations
- Selective: >1,000x more selective for TRK over 98% of 226 non-TRK kinases
- Activity against acquired **solvent front**, **xDFG**, **gatekeeper**, and TRK mutations demonstrated in enzyme- and cell-based assays and *in vivo* tumour models
- Excellent drug properties: orally dosed, high exposure





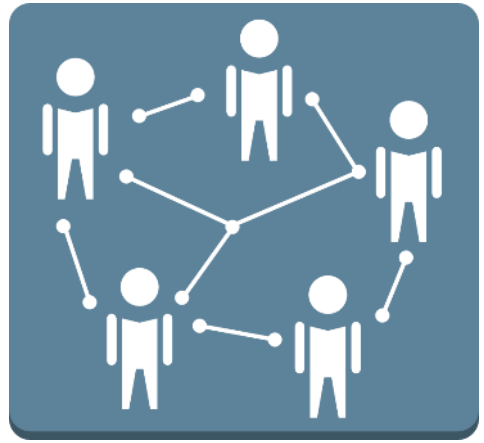
IC_{50}, half maximal inhibitory concentration; TRK, tropomyosin receptor kinase; xDFG, xDFG motif

Drilon A, et al. Cancer Discov. 2017;7:963-72

THANK YOU!

NTRK connect®
POWERED BY COR2ED

- **Thank you** for your participation and input during this meeting, slides will be made available for download.



- Please complete the **post-meeting survey**

- **Honorarium forms** can be submitted via the COR2ED Engage meeting page

NTRK connect®
POWERED BY COR2ED

NTRK CONNECT
Bodenackerstrasse 17
4103 Bottmingen
SWITZERLAND

Dr. Froukje Sosef MD

+31 6 2324 3636

froukje.sosef@cor2ed.com

Dr. Antoine Lacombe Pharm D, MBA

+41 79 529 42 79

antoine.lacombe@cor2ed.com

Heading to the heart of Independent Medical Education Since 2012