NTRK connect®

POWERED BY COR2ED

HIGHLIGHTS BY

Dr. Fernando Santini

Memorial Sloan Kettering Westchester
West Harrison, NY, USA

MAY 2021

DISCLOSURES

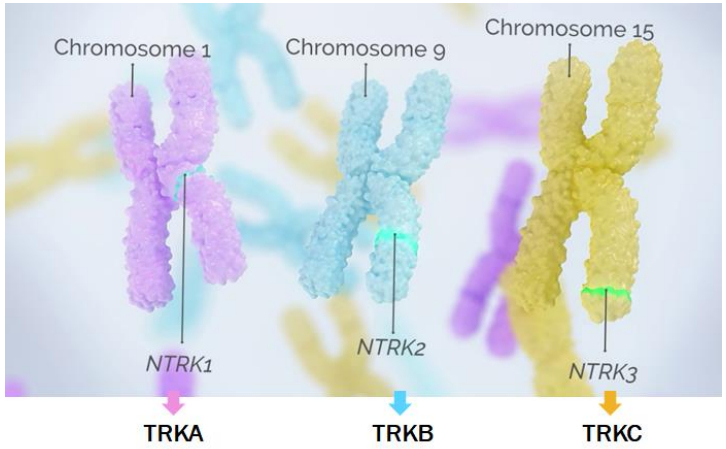
- Please note: Views expressed within this presentation are the personal opinions of the author. They do not necessarily represent the views of the author's academic institution or the rest of NTRK CONNECT group.

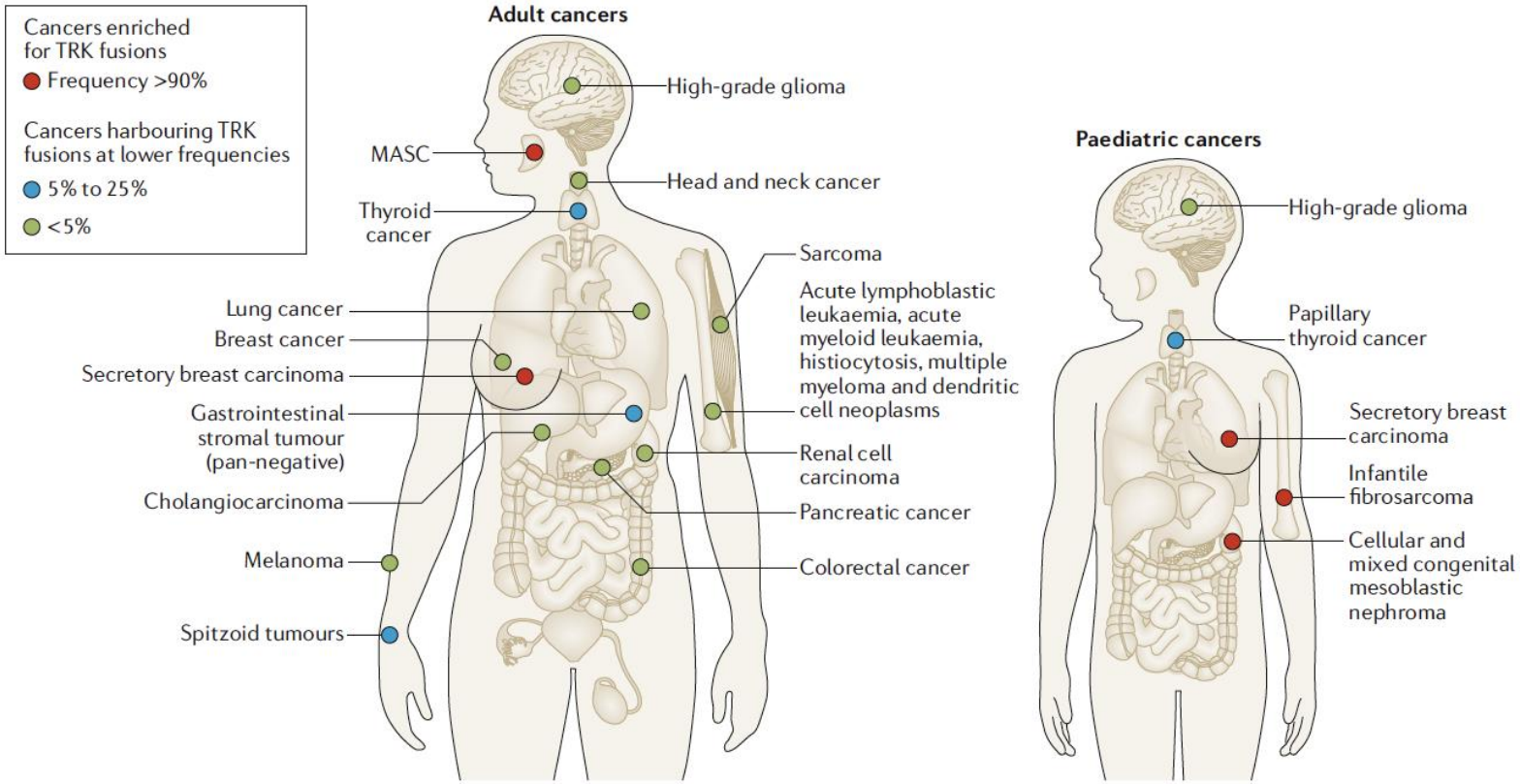
- This content is supported by an independent educational grant from Bayer.

- **Disclosures**: Dr Santini has received honoraria from the following: AstraZeneca, Bayer, BMS, Eli Lilly, MDHealth, MSD, Novartis and Roche.

EPIDEMIOLOGY OF *NTRK* FUSIONS TUMOURS

NTRK genes family





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

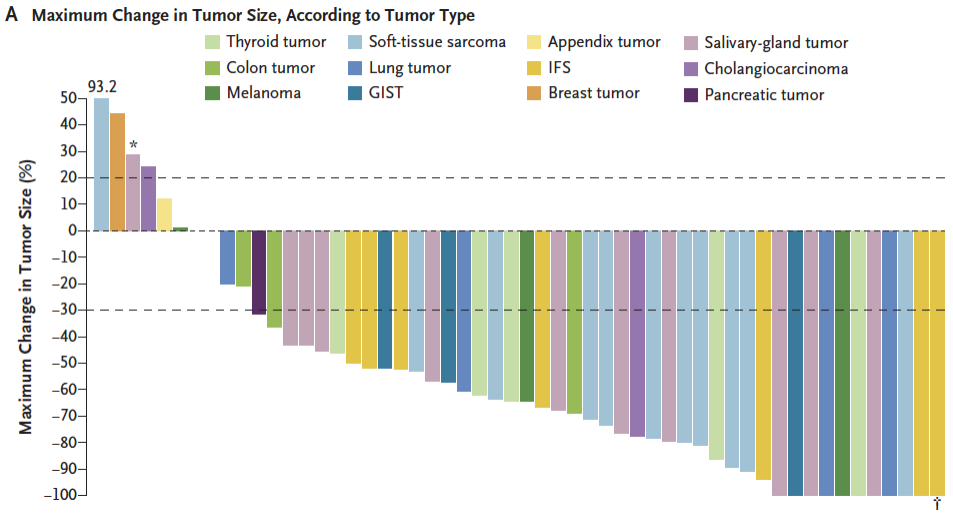
Figure source: Cocco E, et al. Nat Rev Clin Oncol. 2018;15:731-7

INITIAL EFFICACY RESULTS OF APPROVED TRK INHIBITORS RESPONSES BY TUMOUR TYPE

NTRK connect® POWERED BY COR2ED

Larotrectinib[1]

Data cutoff: 17 July 2017

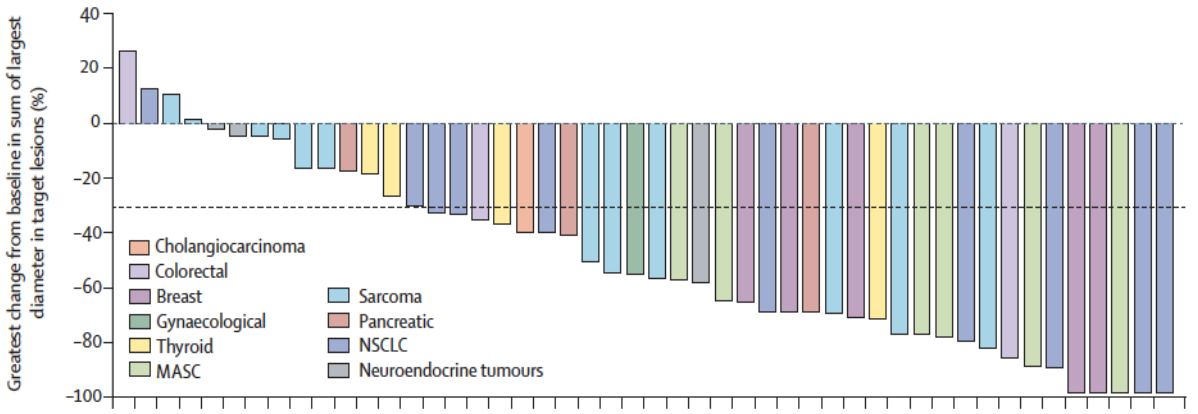


Objective responses with larotrectinib are seen in multiple tumour types and in most of the patients:

80%, 95% CI: 67-90

Entrectinib[2]

Data cutoff: 31 May 2018



Objective responses with entrectinib are seen in multiple tumour types and in most of the patients:

57%, 95% CI: 43.2-70.8

CI, confidence interval; CRC, colorectal cancer; GIST, gastrointestinal stromal tumour; IFS, infantile fibrosarcoma; MASC, mammary analogue secretory carcinoma; NSCLC, non-small-cell lung cancer; TRK, tropomyosin receptor kinase

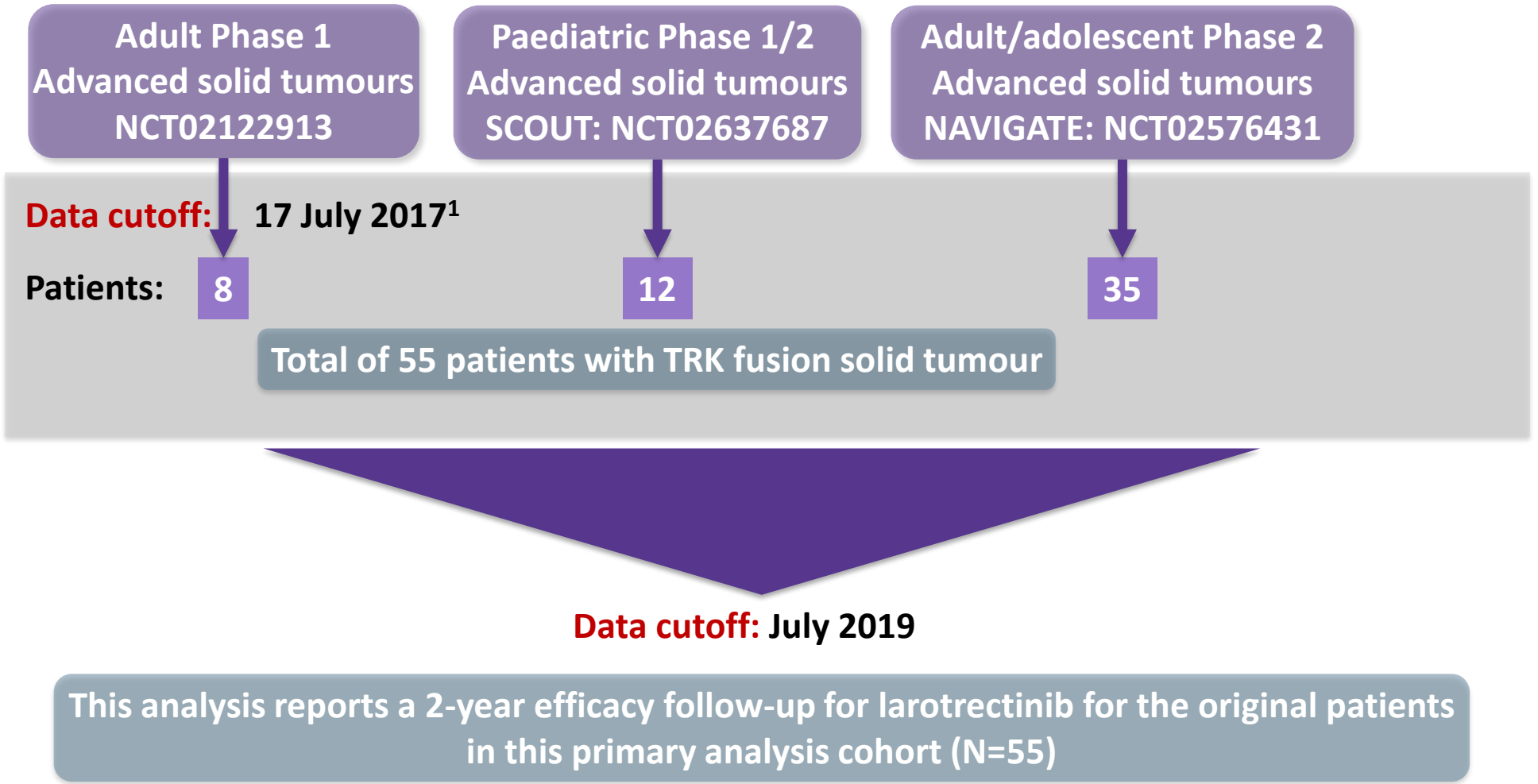
1. Drilon A, et al. N Engl J Med. 2018;378:731-9; 2. Doebele RC, et al. Lancet Oncol 2020;21:271-82

LONG-TERM OUTCOMES OF PATIENTS WITH TRK FUSION CANCER TREATED WITH LAROTRECTINIB

Drilon A. et al. AACR 2021, CT020

TRK, tropomyosin receptor kinase

2-YEAR EFFICACY FOLLOW-UP FOR LAROTRECTINIB



TRK, tropomyosin receptor kinase

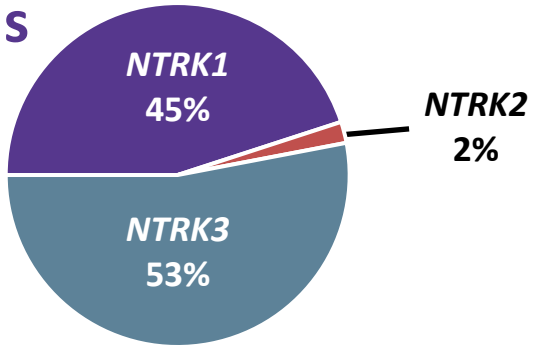
1. Drilon A, et al. N Engl J Med. 2018;378:731-9

BASELINE DEMOGRAPHICS AND DISEASE CHARACTERISTICS IN THE PRIMARY ANALYSIS SET

Characteristics	Primary analysis set (N=55)
Age, median (range), years	45 (0.3-76)
Paediatric (<18 years), n (%)	12 (22)
Adult (≥18 years), n (%)	43 (78)
Female, n (%)	26 (47)
Male, n (%)	29 (53)
ECOG performance status, n (%)	
0	24 (44)
1	27 (49)
2	4 (7)
Prior cancer treatments, n (%)	
Surgery	48 (87)
Systemic therapy	44 (80)
Radiotherapy	27 (49)
Number of prior systemic therapies, n (%)	
0	11 (20)
1	16 (29)
2	9 (16)
3 or more	19 (35)
Median prior systemic therapies, n (range)	2 (0-10)

Primary tumours type, n (%)	Primary analysis set (N=55)
Salivary gland	12 (22)
Soft tissue sarcoma*	11 (20)
IFS	7 (13)
Thyroid	5 (9)
Melanoma	4 (7)
Lung	4 (7)
Colon	4 (7)
GIST	3 (5)
Cholangiocarcinoma	2 (4)
Pancreas	1 (2)
Appendix	1 (2)
Breast	1 (2)

NTRK gene fusions



- Distribution of primary tumours type is very similar to real world data

*Subtypes of soft tissue sarcoma include myopericytoma (n=2), peripheral-nerve sheath tumour (n=2), spindle-cell tumour (n=3), infantile myofibromatosis (n=1), inflammatory myofibroblastic tumour of the kidney (n=1), and sarcoma that was not otherwise specified (n=2).

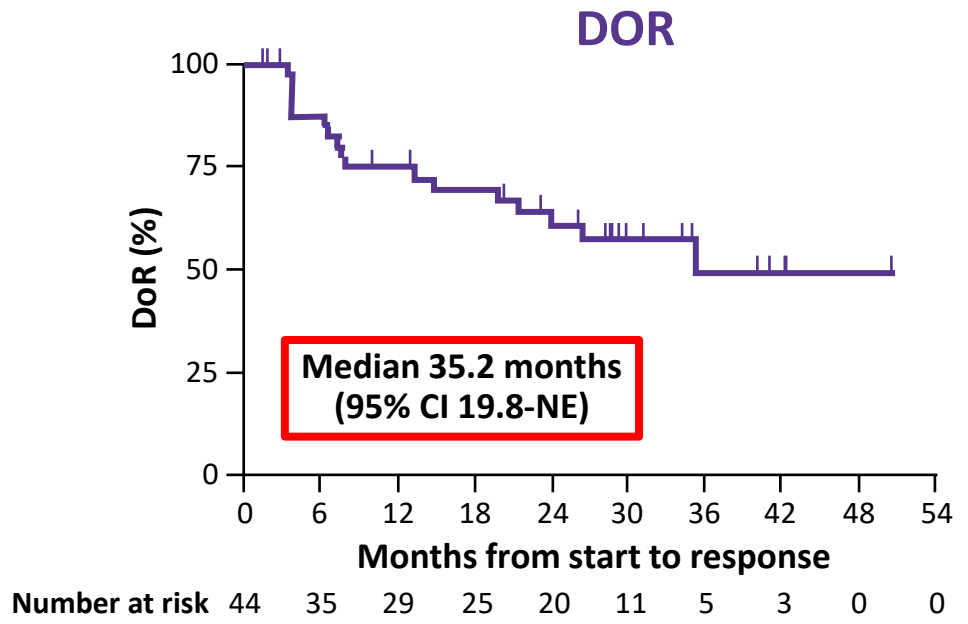
ECOG, Eastern Cooperative Oncology Group; GIST, gastrointestinal stromal tumour; IFS, infantile fibrosarcoma; NTRK, neurotrophic tyrosine receptor kinase; TRK, tropomyosin receptor kinase

1. Drilon A, et al. N Engl J Med. 2018;378:731-9

ROBUST AND DURABLE RESPONSE OF LAROTRECTINIB

RESPONSE RATES OF THE PRIMARY ANALYSIS SET (N=55)		
	Original analysis (July 2017)[1]	2-year follow up (July 2019)
Best overall response		
CR, n (%)	9 (16)	13 (24)
PR, n (%)	35 (64)	31 (56)
SD, n (%)	5 (9)	5 (9)
PD, n (%)	6 (11)	6 (11)
ORR, n (%)	44 (80)	44 (80)
95% CI	67-90	67-90

- Over 2 years' follow-up, the best overall response of 4 patients (7%) improved from a PR to a CR



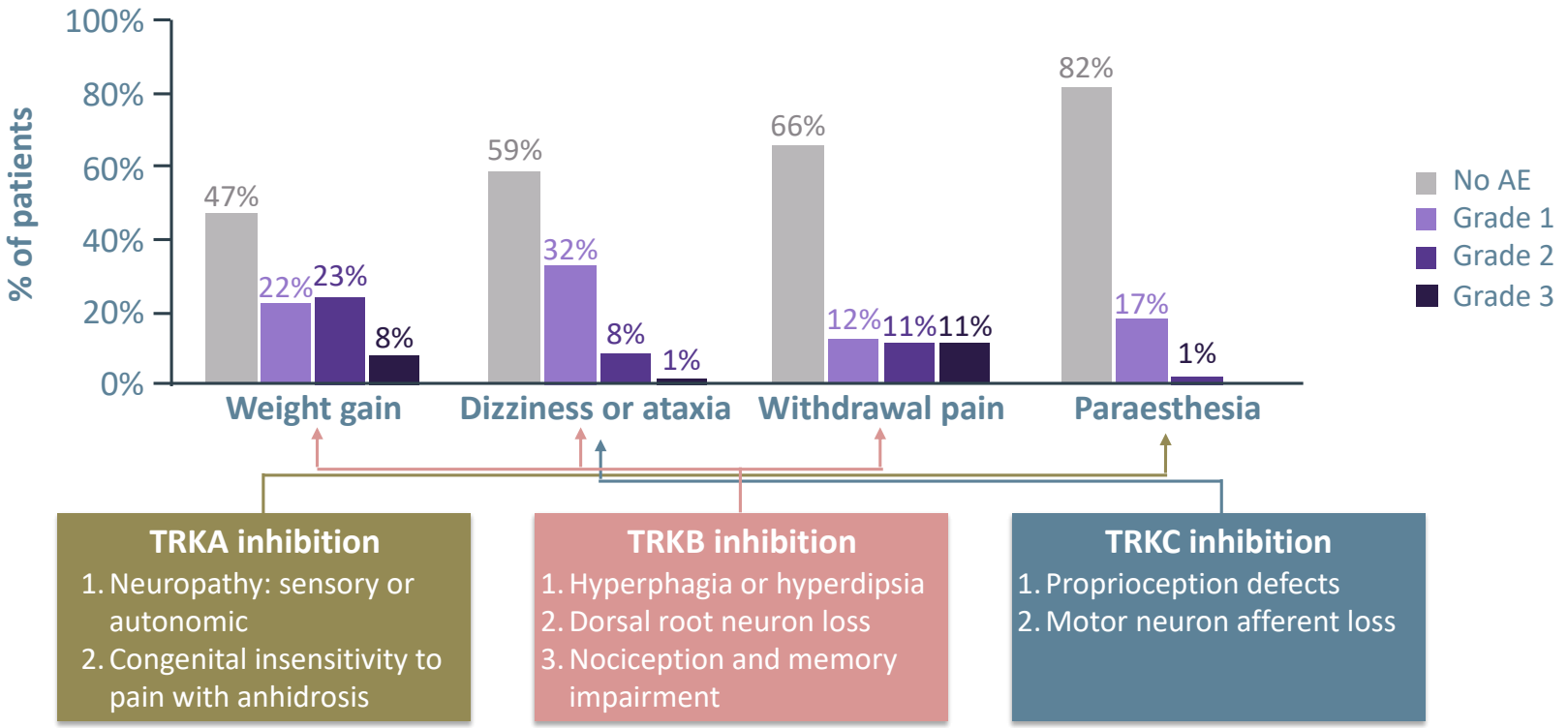
	PATIENTS WITH OBJECTIVE RESPONSE (N=44)
24-month DoR, % (95% CI)	61 (45-77)
Median follow-up	29.3 months

CI, confidence interval; CR, complete response; DoR, duration of response; NE, not estimable; PD, progressive disease; PR; partial response; SD, stable disease

1. Drilon A, et al. N Engl J Med. 2018;378:731-9

SAFETY PROFILE OF LAROTRECTINIB

- Larotrectinib has a favourable safety profile with **no new or unexpected** safety findings over longer follow-up
- Understanding the on-target AEs with TRK inhibition is key:



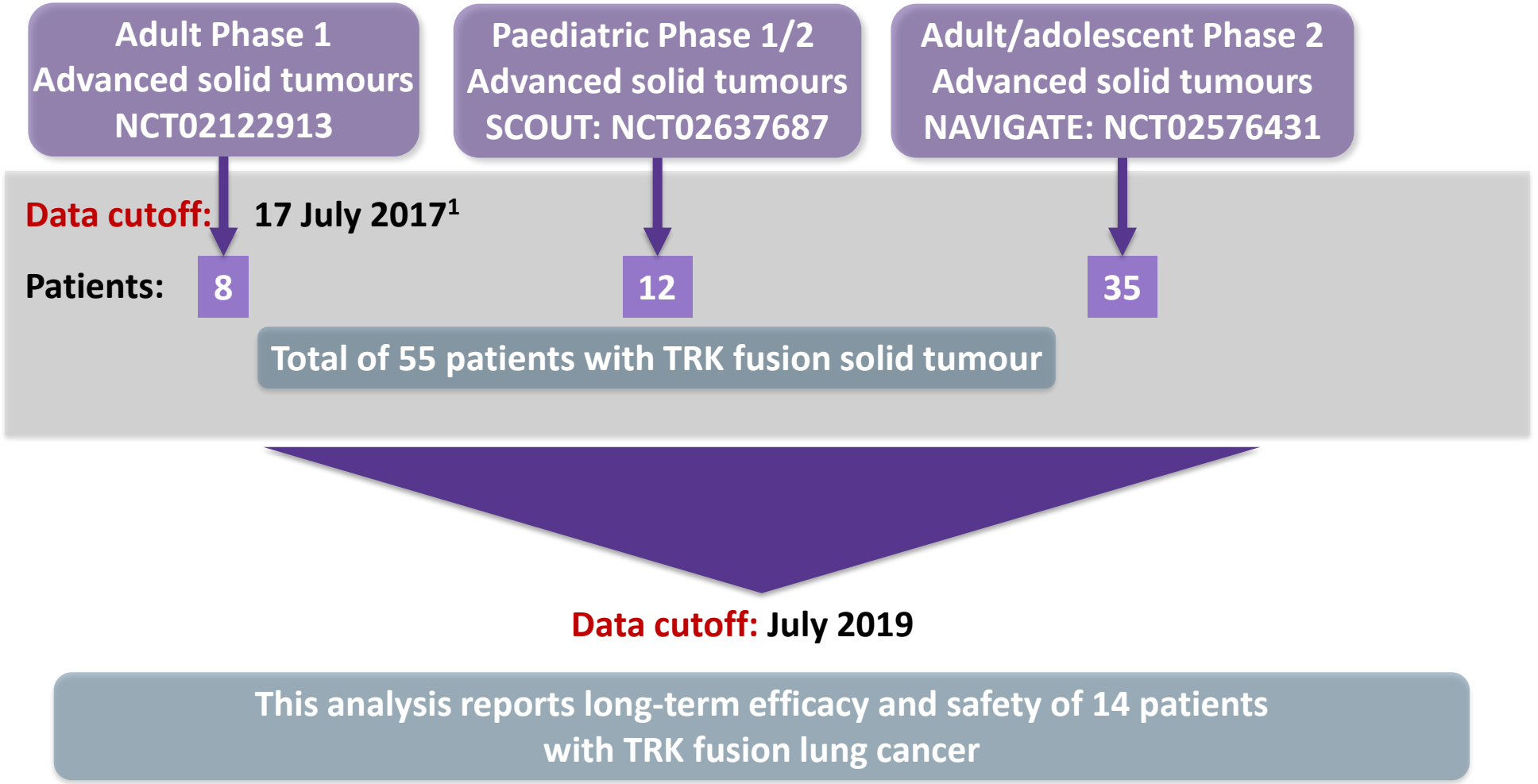
AE, adverse event; TRK, tropomyosin receptor kinase
Source figure: Liu D. et al. Ann Oncol. 2020;31:1207-15

LONG-TERM EFFICACY AND GENOMIC CHARACTERISTICS OF PATIENTS WITH TRK FUSION LUNG CANCER TREATED WITH LAROTRECTINIB

Moreno V. et al. J Thorac Oncol. 2021;16(Suppl_4):S748-S802
European Lung Cancer Congress (ELCC) 2021. Abstract #162P

TRK, tropomyosin receptor kinase

2-YEAR EFFICACY FOLLOW-UP FOR LAROTRECTINIB IN TRK FUSION LUNG TUMOURS



TRK, tropomyosin receptor kinase

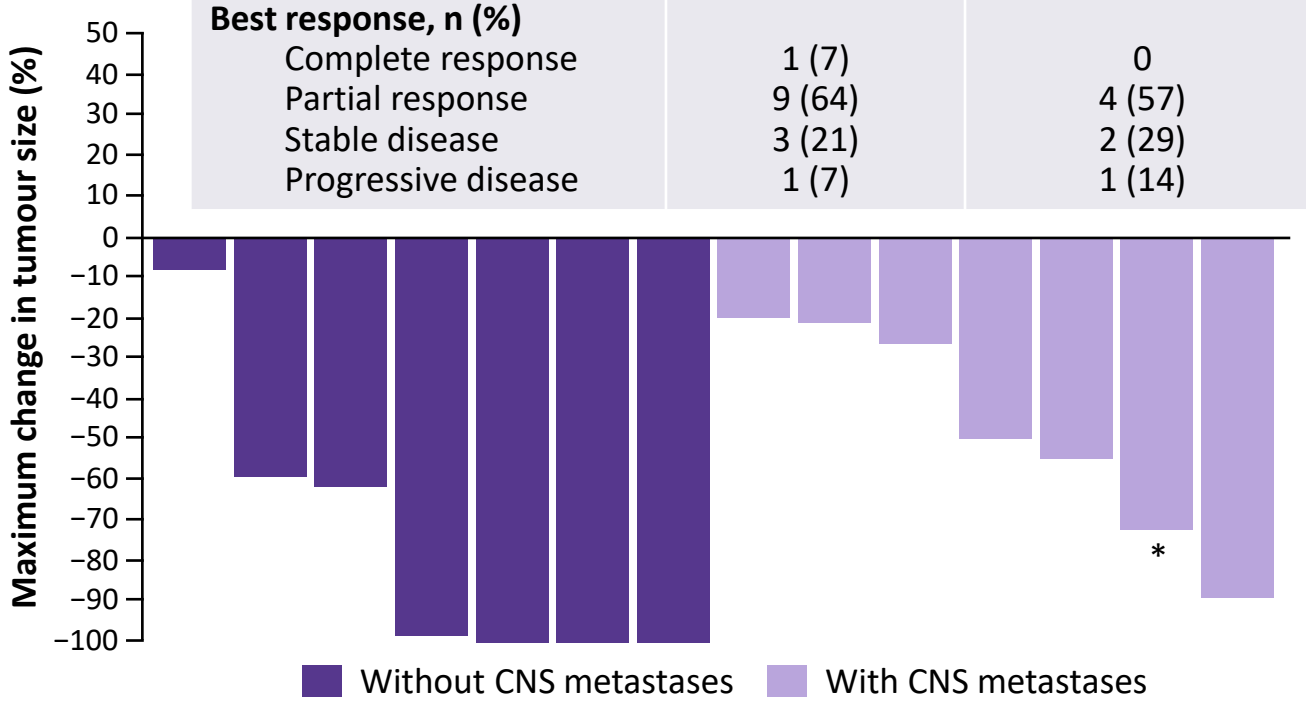
1. Drilon A, et al. N Engl J Med. 2018;378:731-9

DURABLE ANTITUMOUR RESPONSES OF LAROTRECTINIB IN PATIENTS WITH OR WITHOUT CNS METASTASES

- ORR was **71%** (95% CI 42-92)
- ORR for the patients with baseline **CNS metastases** was **57%** (95% CI 18-90)
- One patient with intracranial measurements had **100% reduction in CNS lesions by cycle 4**

MAXIMUM CHANGE IN TUMOUR SIZE FOLLOWING TREATMENT IN PATIENTS WITH TRK FUSION LUNG CANCER

	All patients (N=14)	Patients with CNS metastases (n=7)
Objective response rate, % (95% CI)	71 (42-92)	57 (18-90)
Best response, n (%)		
Complete response	1 (7)	0
Partial response	9 (64)	4 (57)
Stable disease	3 (21)	2 (29)
Progressive disease	1 (7)	1 (14)



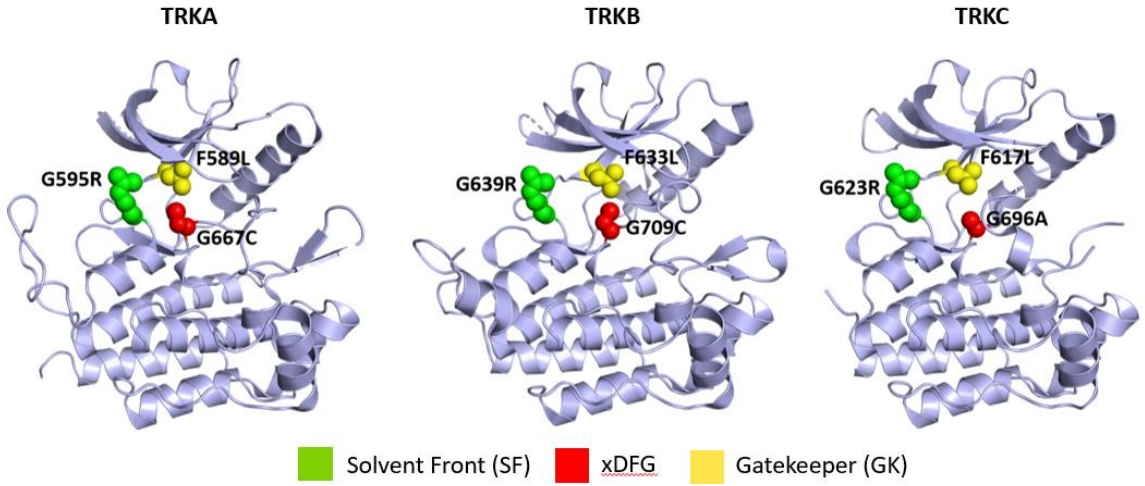
* Patient had 100% reduction in CNS lesions

CI, confidence interval; CNS, central nervous system; ORR, objective response rate; TRK, tropomyosin receptor kinase

MECHANISMS OF RESISTANCE NEED FURTHER EVALUATION AFTER DISEASE PROGRESSION

CO-OCCURRING GENOMIC ALTERATIONS AT BASELINE

Type of alteration	Genes affected
Loss of function	*CDKN2A/B* (n=3) *MTAP* (n=1)
Amplification	*HGF, PIK3C2B, CDK6, MDM4, ZNF217 CNV* (n=1 each)
Mutation	*TP53* (n=3) *CTNNB1* (n=2) *FANCL*, *RB1*, *TERT* promoter, *IRF1*, *MTOR, NRAS, SP3B1, PIK3C2B, MAP2K4* (n=1 each)



GENOMIC PROFILING OF NSCLC PATIENTS WHO PROGRESSED ON LAROTRECTINIB

Patient number	Best response	On-target *NTRK* mutations	Other genomic alterations
Patient 1	Stable disease	*NTRK1* SF G595R xDFG G667S	*KRAS* D57N and amplifications in *BRAF, MET* and *EGFR*
Patient 2	Partial response	*NTRK1* SF G595R GK F589L	None
Patient 3	Progressive disease	*NTRK1* GK F589L	*KRAS* G12D
Patient 4	Stable disease	None	None

CNV, copy number variation; EGFR, epidermal growth factor receptor; NSCLC, non-small-cell lung cancer; NTRK, neurotrophic tyrosine receptor kinase; TRK, tropomyosin receptor kinase

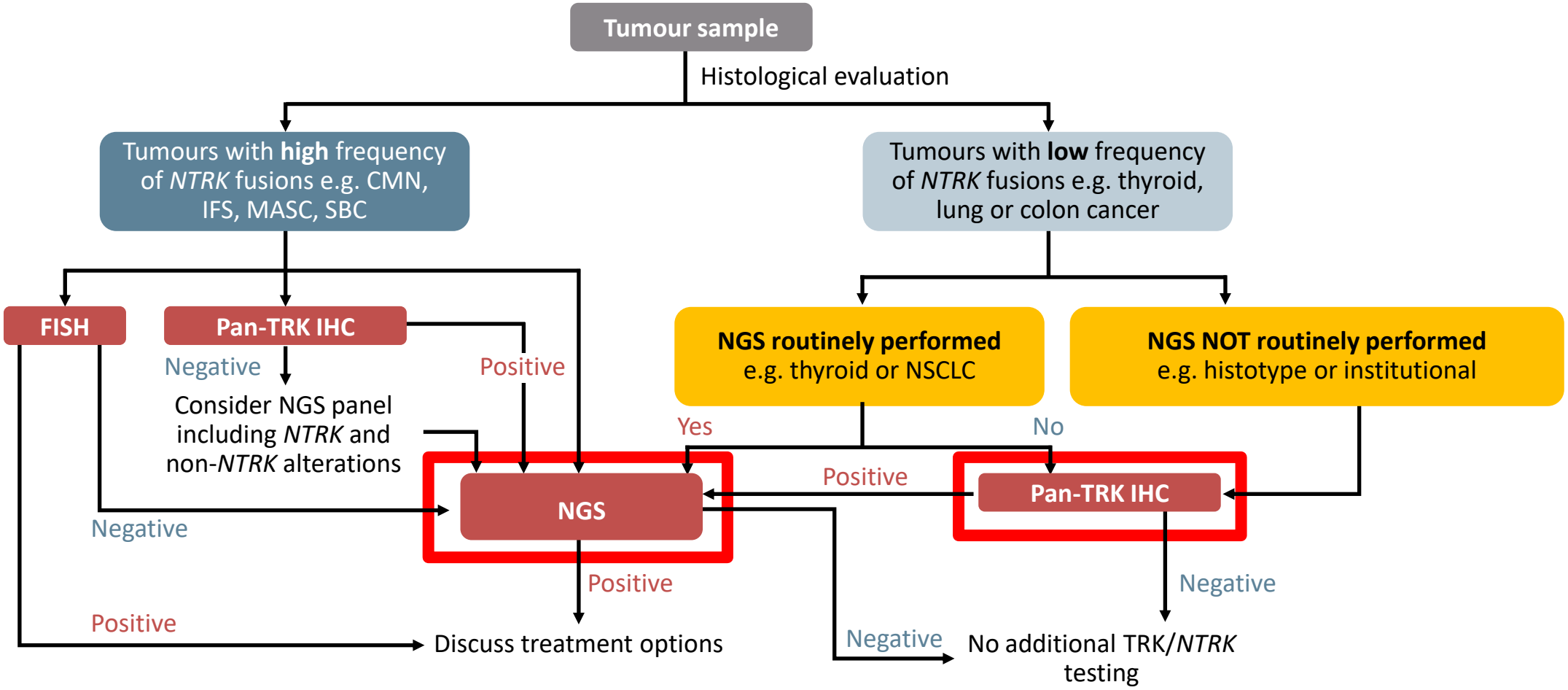
Source figure: Hyman D, et al. AACR2019, CT127

NTRK1 FUSION DETECTION FROM CLINICAL cfDNA NGS USING A *DE NOVO* FUSION CALLER

Yablonovitch A. et al. AACR 2021, #537

cfDNA, circulating free DNA; NGS, next-generation sequencing; NTRK, neurotrophic tyrosine receptor kinase

BACKGROUND: TESTING ALGORITHM FOR TRK FUSION CANCER

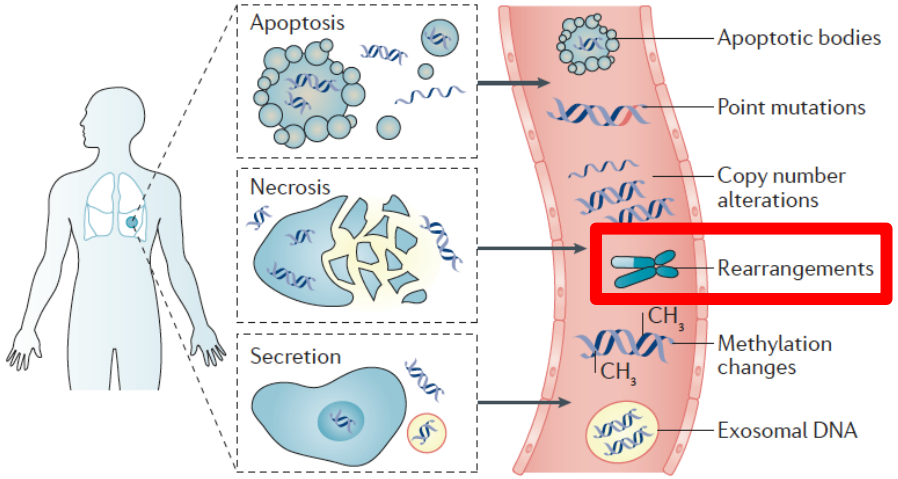


CMN, congenital mesoblastic nephroma; FISH, Fluorescent in situ hybridization; IHC, immunohistochemistry; IFS, infantile fibrosarcoma; NSCLC, non-small-cell lung cancer; MASC, mammary analogue secretory carcinoma; NGS, next-generation sequencing; NTRK, neurotrophic tyrosine receptor kinase; SBC, Secretory breast carcinoma; TRK, tropomyosin receptor kinase

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

DE NOVO FUSION CALLER: BACKGROUND-METHODS

NTRK rearrangements = clinically actionable targets



Cohort of 23’280 patients
276 healthy samples (control)
1’199 patients with *ERBB2* amps (negative control)

Tested with Guardant360 (liquid biopsy NGS-based array)
Reanalysed using the novel algorithm

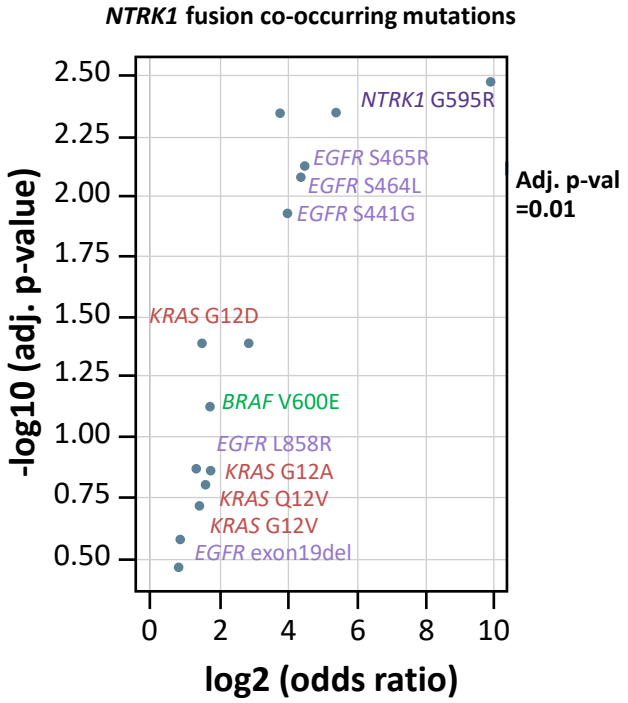
DE NOVO FUSION CALLER EXHIBITS HIGH SPECIFICITY

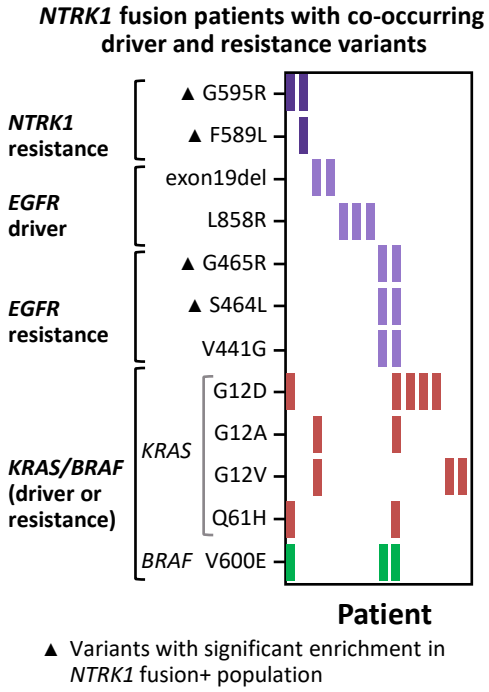
Negative control cohort	Sample #	#*NTRK1* fusions	Specificity
Healthy controls	276	0	100%
ERBB2 amp+ patients	1’199	3	>99%

Amps, amplifications; ERBB2, Erb-B2 Receptor Tyrosine Kinase 2; NGS; next-generation sequencing; NTRK, neurotrophic tyrosine receptor kinase

NTRK1 FUSION DETECTION USING A *DE NOVO* FUSION CALLER: RESULTS

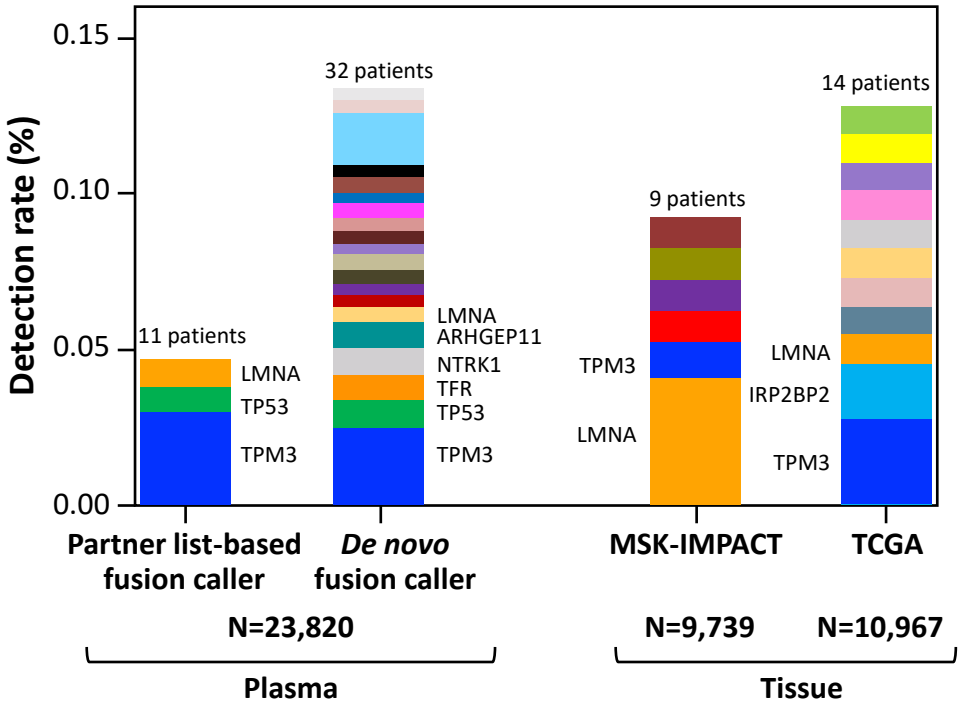
Patients with *NTRK1* fusions have co-occuring known driver and resistance mutations





▲ Variants with significant enrichment in *NTRK1* fusion+ population

NTRK1 fusions prevalence is comparable to tissue and most partners are unique to individual patients



- **Conclusion:** *de novo* fusion caller assay can increase the yield for the detection of *NTRK1* fusions in cfDNA

EGFR, epidermal growth factor receptor; MSK-IMPACT, Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets; NTRK, neurotrophic tyrosine receptor kinase; TCGA, The Cancer Genome Atlas

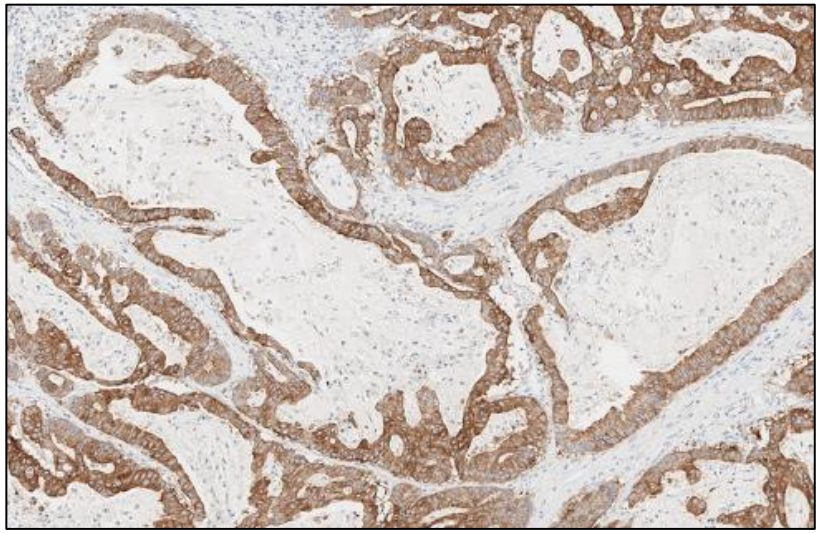
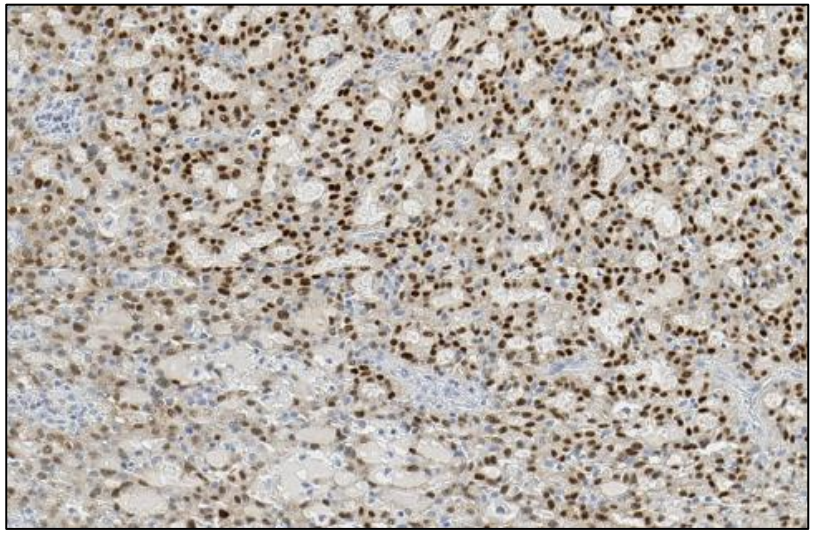
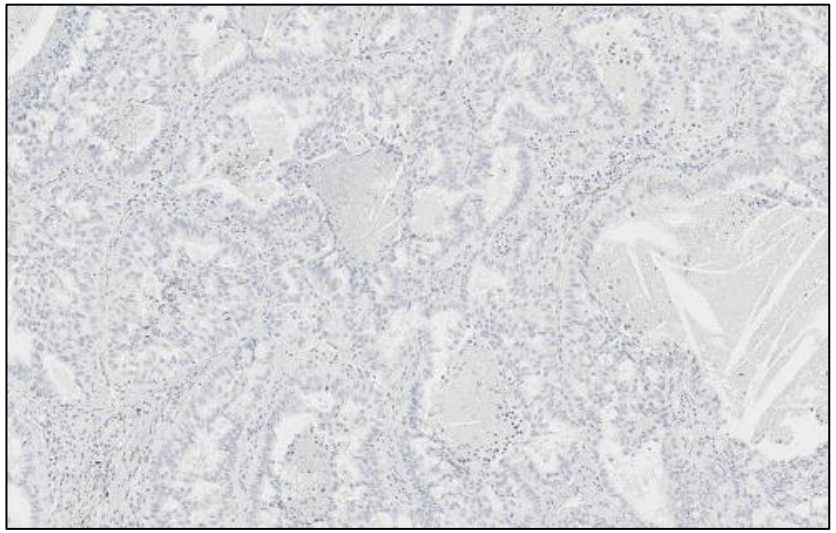
IMMUNOHISTOCHEMICAL DETECTION OF PAN-TRK EXPRESSION IN SOLID TUMOR SPECIMENS: INTER-LABORATORY AND INTER-READER AGREEMENT IN NGS-CONFIRMED NTRK FUSION-POSITIVE AND FUSION-NEGATIVE CASES

Stratton S. et al. USCAP 2021, #420

NGS, next-generation sequencing; NTRK, neurotrophic tyrosine receptor kinase; TRK, tropomyosin receptor kinase

PAN-TRK IHC STAINING IN DIFFERENT TUMOURS

NTRK connect® POWERED BY COR2ED

Colorectal carcinoma (*TPM3-NTRK1*)	Secretory carcinoma of salivary gland (*ETV6-NTRK3*)	NSCLC (fusion negative)
		

- Sample images demonstrating variable patterns of VENTANA pan-TRK (EPR17341) Assay in different tumours types

ETV6, ETS Variant Transcription Factor 6; IHC, immunohistochemistry; NSCLC, non-small-cell lung cancer; NTRK, neurotrophic tyrosine receptor kinase; TPM3, tropomyosin 3; TRK, tropomyosin receptor kinase

CONCLUSIONS

- **Overall agreement between readers was high (overall OPA=92.6%), but varied based on fusion partner and staining pattern observed with this analytic assay**

- **Staining tissue location** did not contribute to variance in reader scoring

- Conclusions regarding concordance and **cutoffs** should not be drawn from this data as this limited study was not designed to determine a cutoff

IHC; immunohistochemistry; ETV6, ETS Variant Transcription Factor 6; NGS, next-generation sequencing; NSCLC, non-small-cell lung cancer; NTRK, neurotrophic tyrosine receptor kinase; OPA, Overall Percent Agreement; ROC, receiver operating characteristic; TRK, tropomyosin receptor kinase

IN SUMMARY

- **Larotrectinib** continues to demonstrate a **robust and durable** response rate with extended survival benefits in adult and paediatric patients with TRK fusion cancer regardless of tumour type

- **Mechanisms of resistance** should be further understood in order to develop the **next-generation TRK inhibitors**

- These data highlight the importance of **identifying *NTRK* gene fusions** in patients with cancer

- **Need to test**, test, test → to identify those patients with TRK fusion positive tumours

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

REACH NTRK CONNECT VIA TWITTER, LINKEDIN, VIMEO & EMAIL OR VISIT THE GROUP'S WEBSITE http://www.ntrkconnect.info

Follow us on Twitter
@ntrkconnectinfo

Follow the
NTRK CONNECT
group on LinkedIn

Watch us on the
Vimeo Channel
NTRK CONNECT

Email
froukje.sosef
@cor2ed.com

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

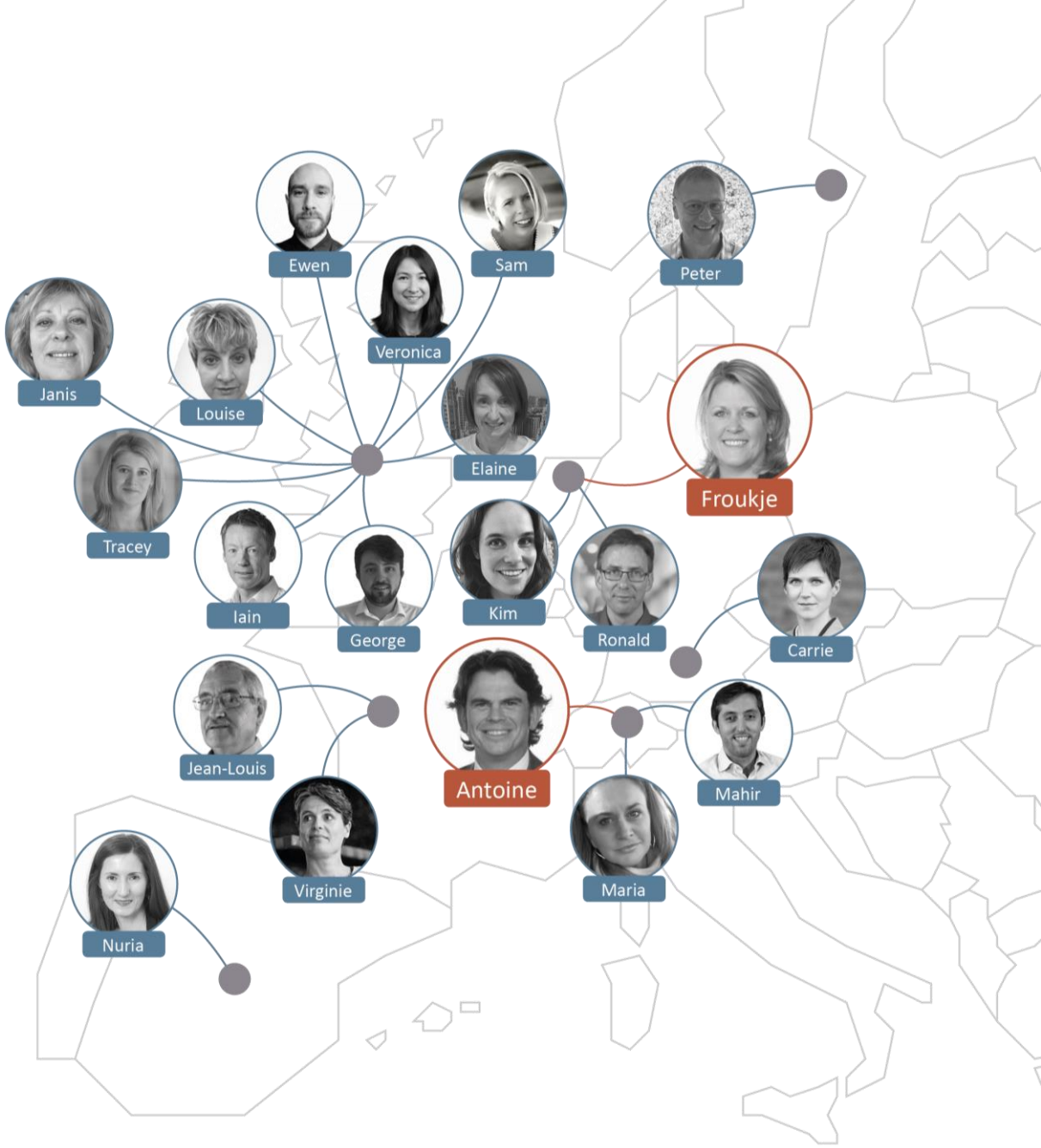
antoine.lacombe@cor2ed.com

Connect on
LinkedIn @NTRK CONNECT

Watch on
Vimeo @NTRK CONNECT

Visit us at
ntrkconnect.info

Follow us on
Twitter @ntrkconnectinfo



Heading to the heart of Independent Medical Education Since 2012