



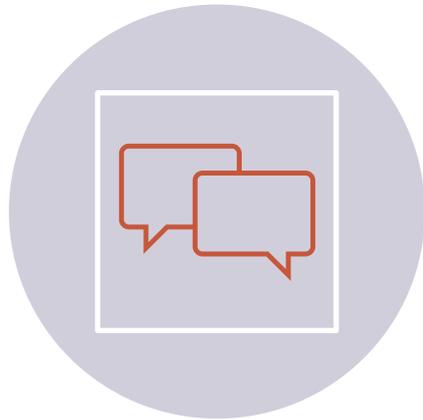
# EXPERTS KNOWLEDGE SHARE

## DIAGNOSING AND TREATING TRK FUSION-POSITIVE CANCER

Caterina Marchiò, David Hong and Philipp Ivanyi

11<sup>th</sup> September 2022

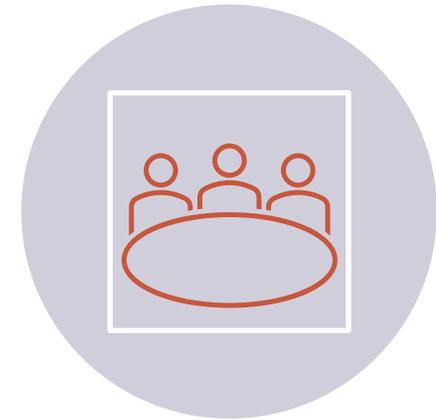
## THE OBJECTIVE OF THIS MEETING IS TO HAVE A PRACTICAL AND CASE-BASED DISCUSSION ABOUT TRK FUSION-POSITIVE CANCER



YOUR OPPORTUNITY TO **DISCUSS AND SHARE LEARNINGS ON DIAGNOSIS AND TREATMENT** OF TRK FUSION-POSITIVE CANCER



A CHANCE TO **LEARN FROM THE EXPERIENCE OF EXPERTS** AND ASK QUESTIONS THAT ARE IMPORTANT TO YOU



DISCUSS **PATIENT CASE STUDIES AND QUESTIONS** THAT YOU MAY HAVE FROM YOUR PRACTICES/INSTITUTIONS

# INTRODUCING THE SCIENTIFIC COMMITTEE



**Caterina Marchiò**

University of Turin, Turin , Italy



**David Hong**

University of Texas MD Andersen Cancer  
Center, Houston, TX, USA



**Philipp Ivanyi**

Hannover Medical School, Hannover,  
Germany

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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.

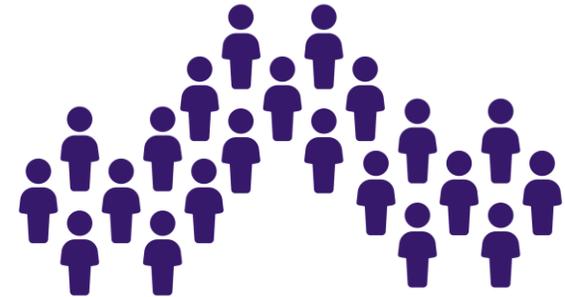
# TODAY'S AGENDA

Session	Who	Duration
<b>PLENARY</b> Welcome and introductions		5 mins
1. Diagnostic approaches and a lung cancer case	Caterina Marchiò	25 mins
2. TRK inhibitor therapy and several case studies	David Hong	25 mins
3. A thyroid cancer case	Philipp Ivanyi	25 mins
<b>KEY LEARNINGS &amp; CLOSE</b>	All	5 mins

# INTERNATIONAL PARTICIPATION



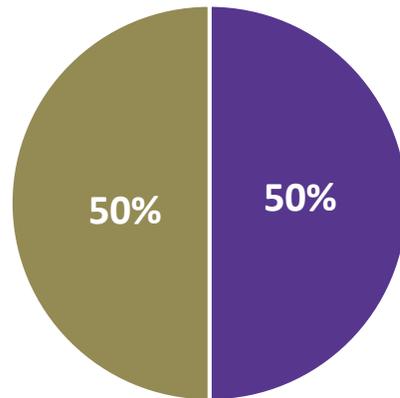
**>30** registrations, spanning **18** countries



- Primarily Oncologists
- Main tumour interests: sarcoma, melanoma, lung, breast, GI and GU cancers

# PARTICIPANT EXPERIENCE AND FIRST LINE TRK INHIBITOR THERAPY CHOICE

Qn: Have you **diagnosed or treated** TRK fusion-positive cancer?



Qn: **First line TRK inhibitor therapy choice?**

**28.6% entrectinib**

**28.6% larotrectinib**

21.4% no experience to date

14.3% other

7.1% no preference



# **A SIMPLE, YET PARADIGMATIC, CASE**

**Caterina Marchiò**

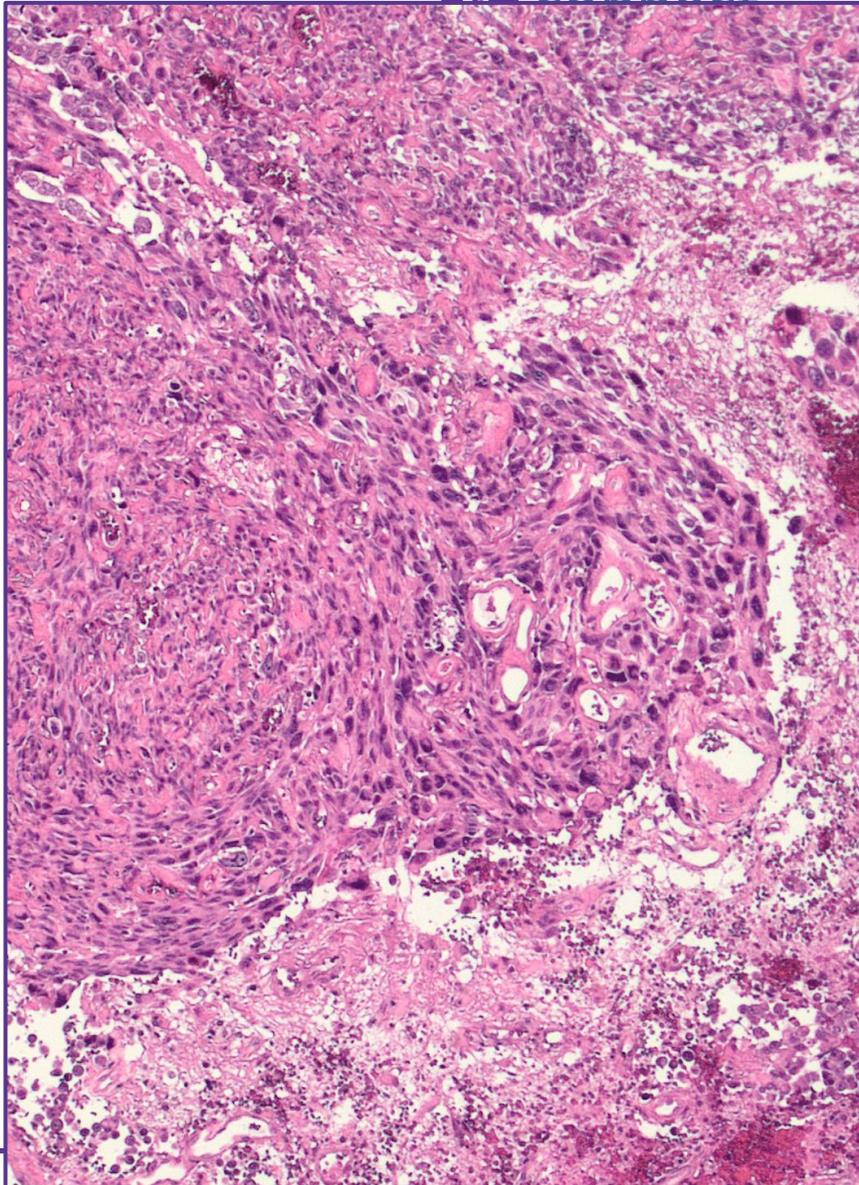
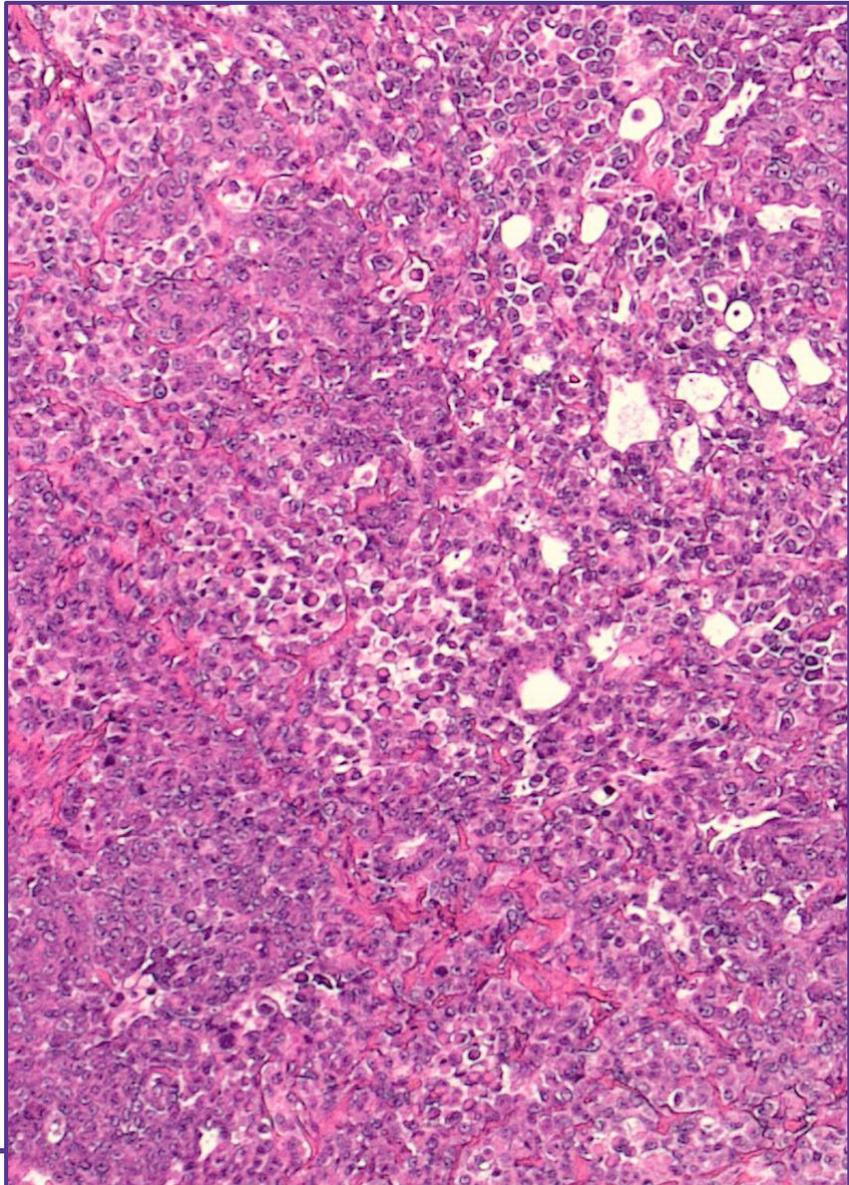
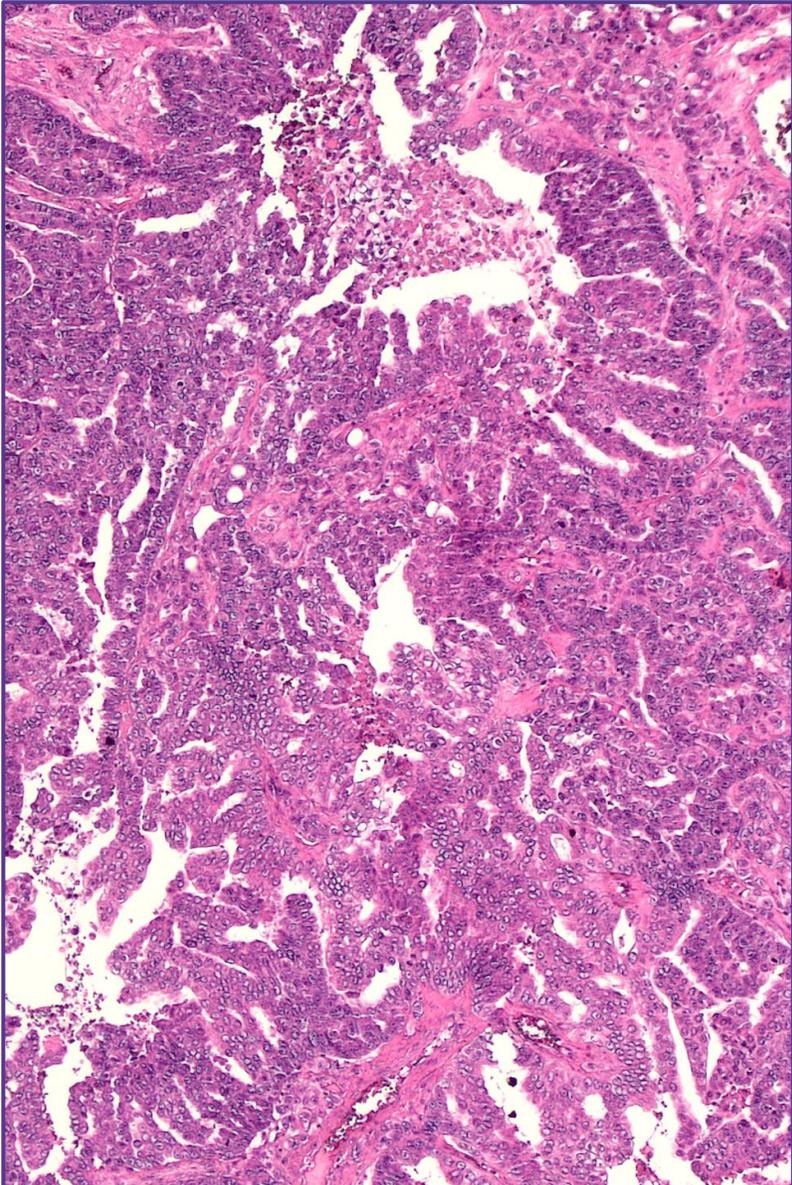
**Dept. of Medical Sciences – University of Turin, Italy  
Pathology Unit, FPO-IRCCS Candiolo**

# DISCLOSURES

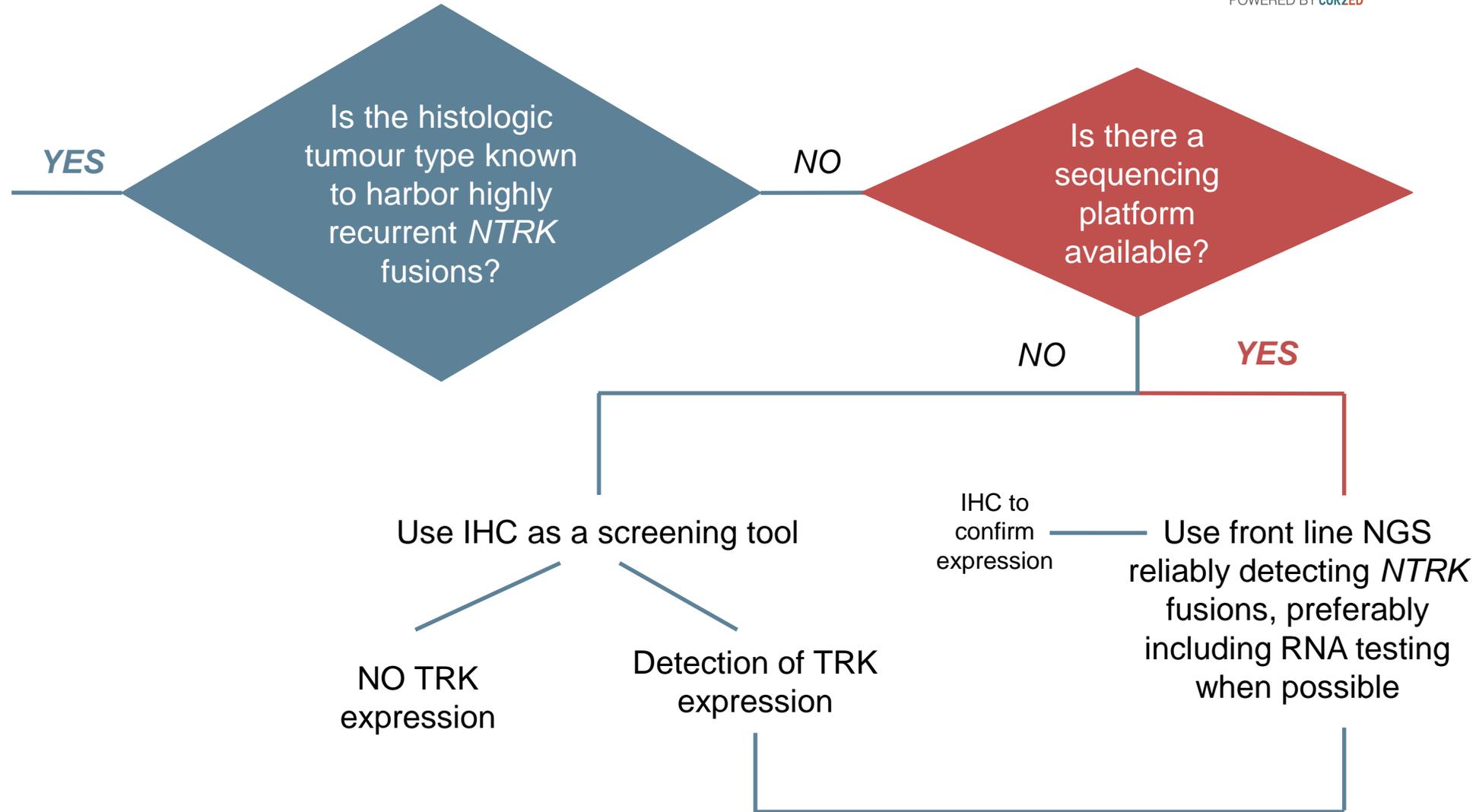
- Consulting role: AstraZeneca, Bayer, Daiichi Sankyo, Roche.

# CASE DESCRIPTION

- Male, 58 yo
- For chest pain and cough -> chest X-ray May 2022: nodular lesion (54 mm diam) in the left lung
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- First lung biopsy Jun 2022 -> non conclusive diagnosis. “Rare atypical elements with sarcomatoid aspects”
- Jun 2022 underwent neurosurgery for brain lesion -> poorly differentiated carcinoma with sarcomatoid features
- Ongoing brain RT on the surgery bed + SBRT on other little single lesion



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



# CASE DESCRIPTION

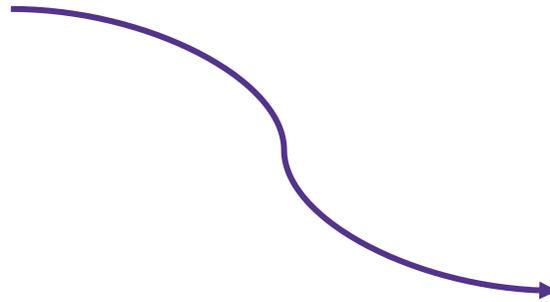
- NGS analysis with a targeted panel of 50 genes (DNA and RNA workflows)
- RNA workflow for gene fusions including *NTRK1*, *NTRK2*, *NTRK3*, *ALK*, *ROS1*, *RET*, *FGFR1*, *FGFR2*, *FGFR3*, *NRG1*



*A TP53-NTRK1 fusion is identified*

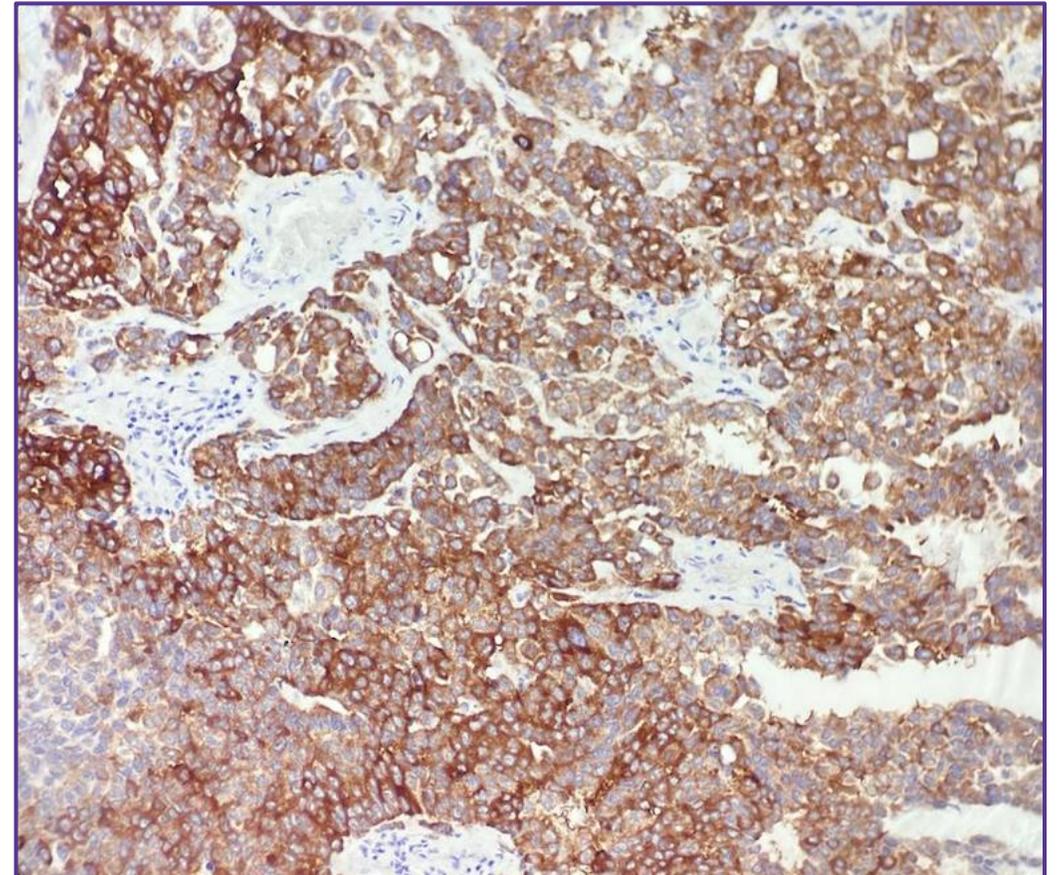
# CASE DESCRIPTION

A *TP53-NTRK1* fusion is identified



Strong and diffuse  
expression demonstrated  
by using a panTRK assay

***Patient will start treatment with TKI (entrectinib)***



# DISCUSSION

## Everything “by the book” – a story of success:

- Team work
- Optimal screening strategy
- Optimal testing algorithm and method

# TEAM WORK – ACKNOWLEDGEMENTS



## ***Dr. Fabrizio Tabbò***

Medical Oncologist, in charge of the patient's care

MD, PhD

Solid background in translational research and Molecular Oncology, with a particular focus on Lung cancer



## ***Prof. Luisella Righi***

Pathologist, in charge of Lung Pathology at a Hub Centre for Lung Cancer

Medical Oncology

MD, PhD

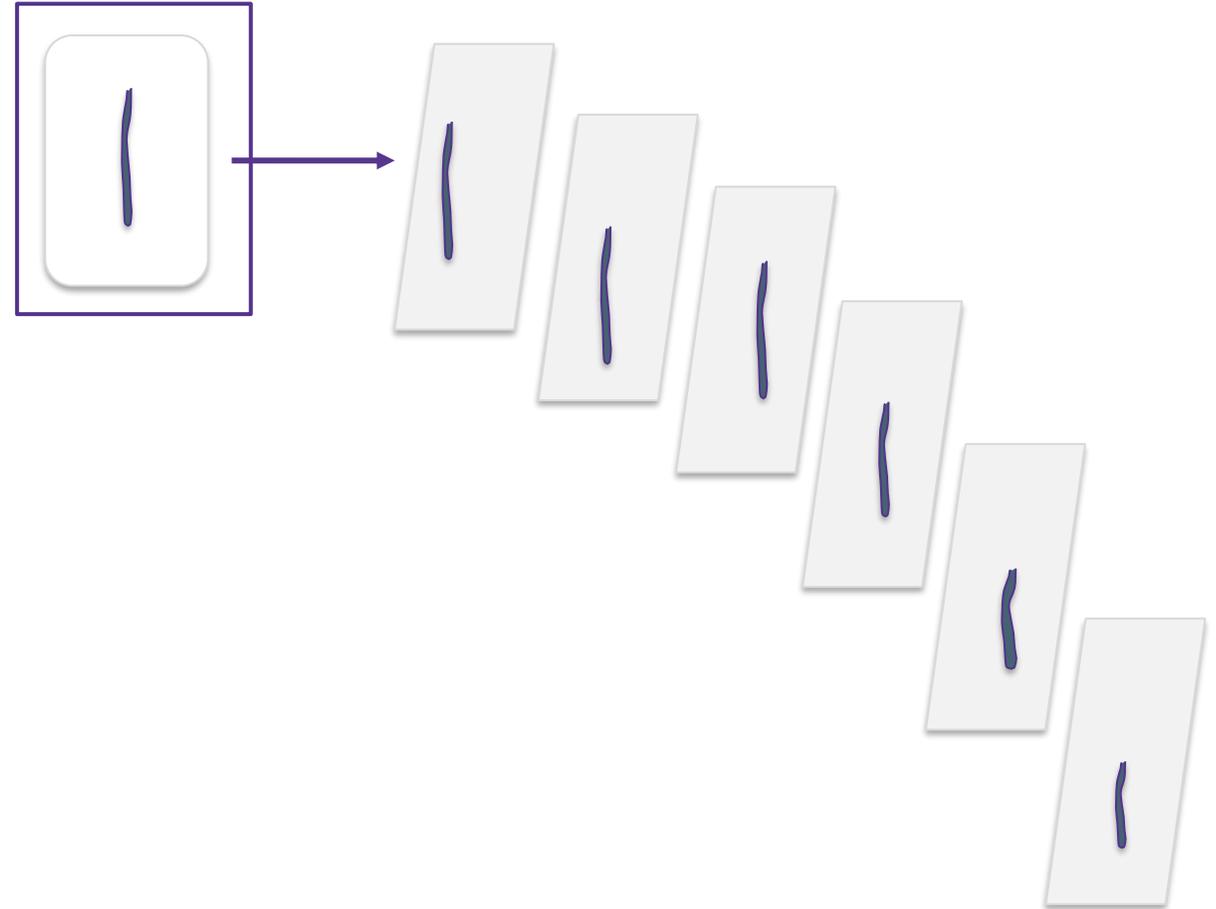
Solid background in translational research and Molecular Pathology



# STRATEGY: ALGORITHM AND METHODS

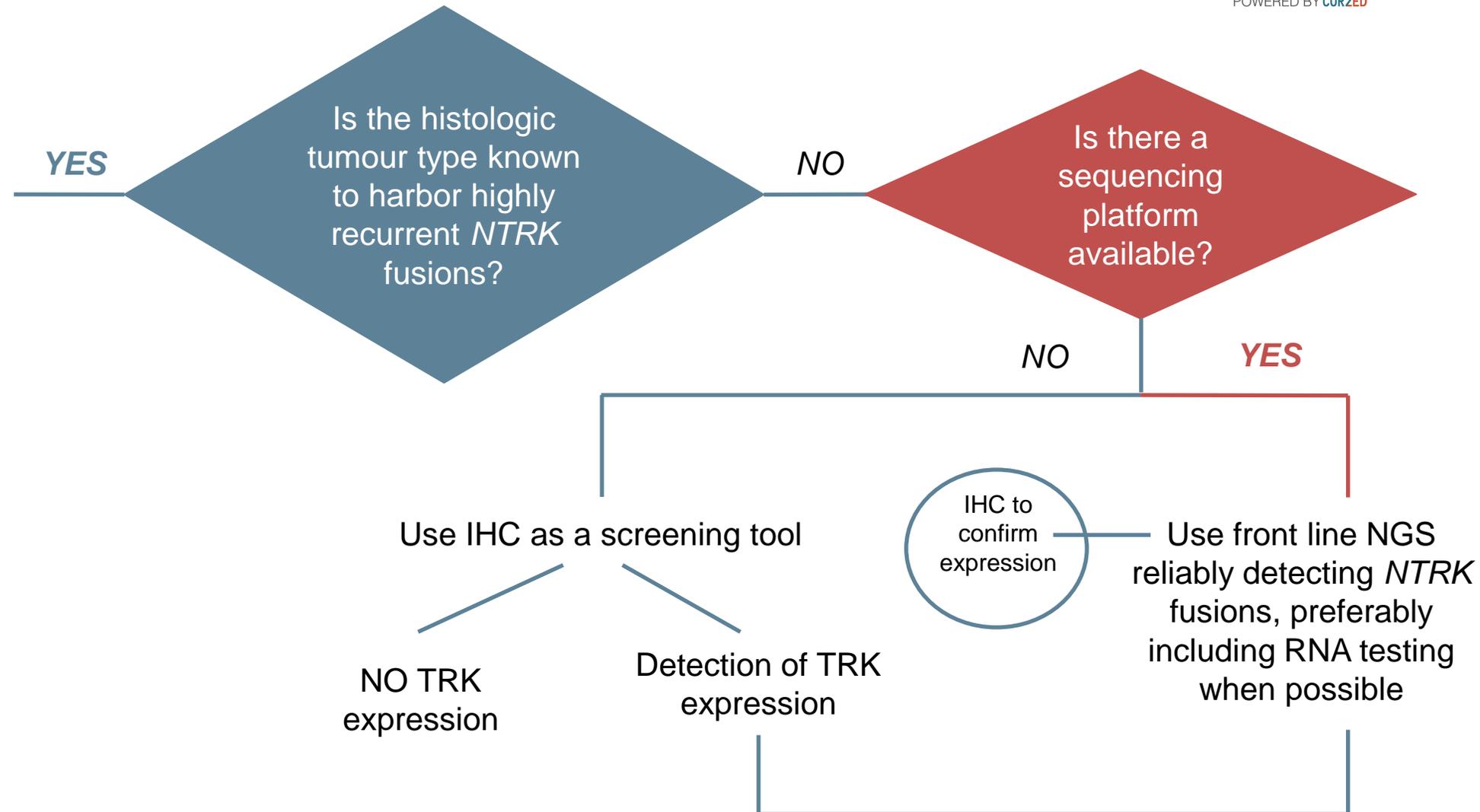
## NSCLC IS THE GOLDEN EXAMPLE FOR MOLECULAR PROFILING

- *EGFR* mutations
- *KRAS* mutations
- *BRAF* mutations
- *MET* exon 14 skipping mutations
- *RET* mutations
- *HER2* mutations
  
- *ALK* fusions
- *ROS1* fusions
- *NTRK1/2/3* fusions
- *RET* fusions
- Neuregulin-1 fusions
  
- PDL1 expression



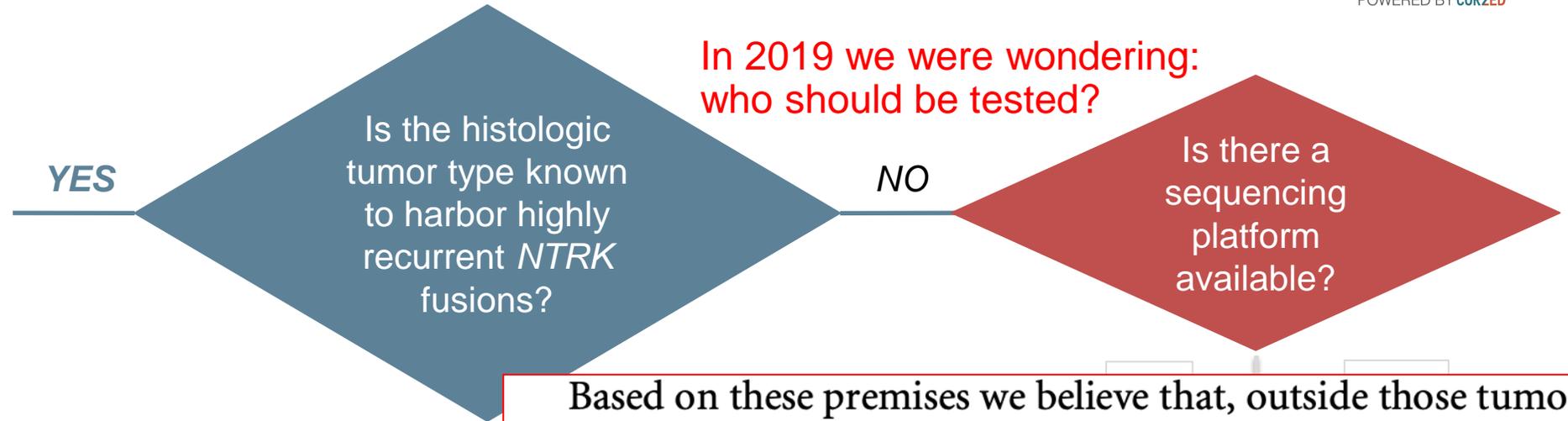
# STRATEGY: ALGORITHM AND METHODS

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



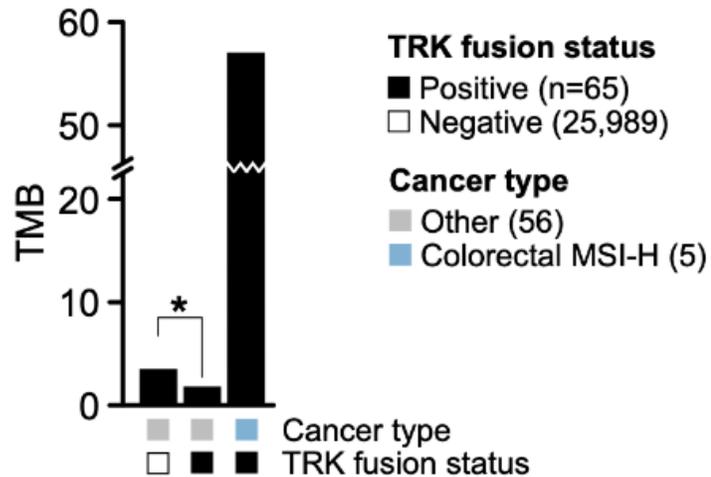
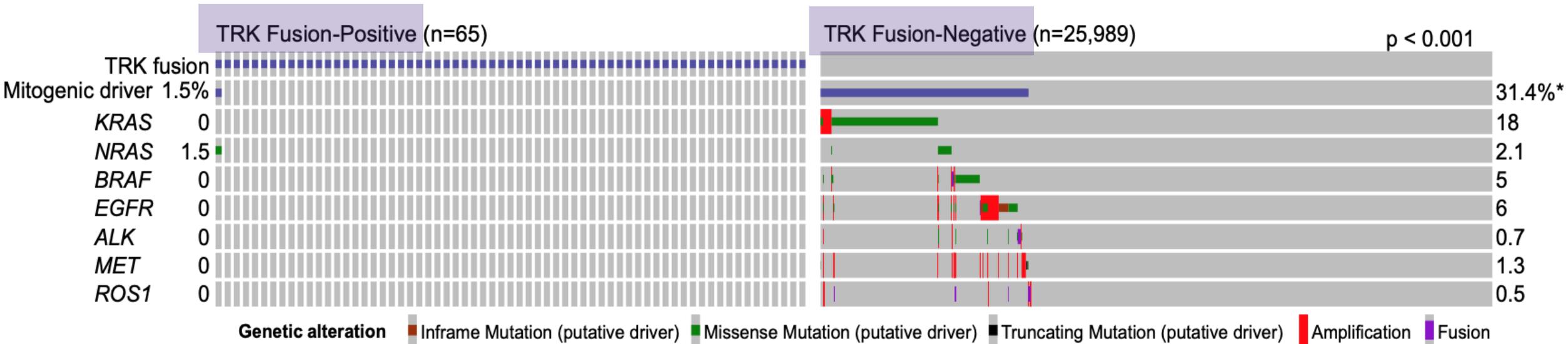
# STRATEGY: ALGORITHM AND METHODS

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



In 2019 we were wondering: who should be tested?

Based on these premises we believe that, outside those tumour types where *NTRK* fusions are expected at high frequency, a more conservative approach for the time being should be applied not to miss patients harbouring these targetable genetic alterations. Therefore, we would argue that the population to be tested should be represented by ‘any malignancy at an advanced stage, in particular if it has been proven wild type for other known genetic alterations tested in routine practice, and especially if diagnosed in young patients’.



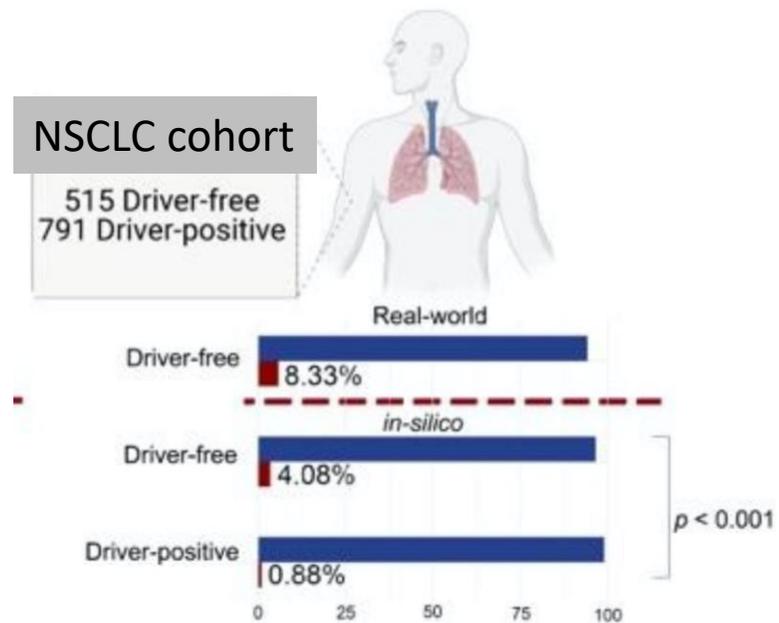
Association between  
*NTRK* fusion and TMB

# Pursuit of Gene Fusions in Daily Practice: Evidence from Real-World Data in Wild-Type and Microsatellite Instable Patients

Berrino E et al, *Cancers* 2021, 13, 3376. <https://doi.org/10.3390/cancers13133376>

12.3% of fusion detection in colorectal carcinomas that are MSI

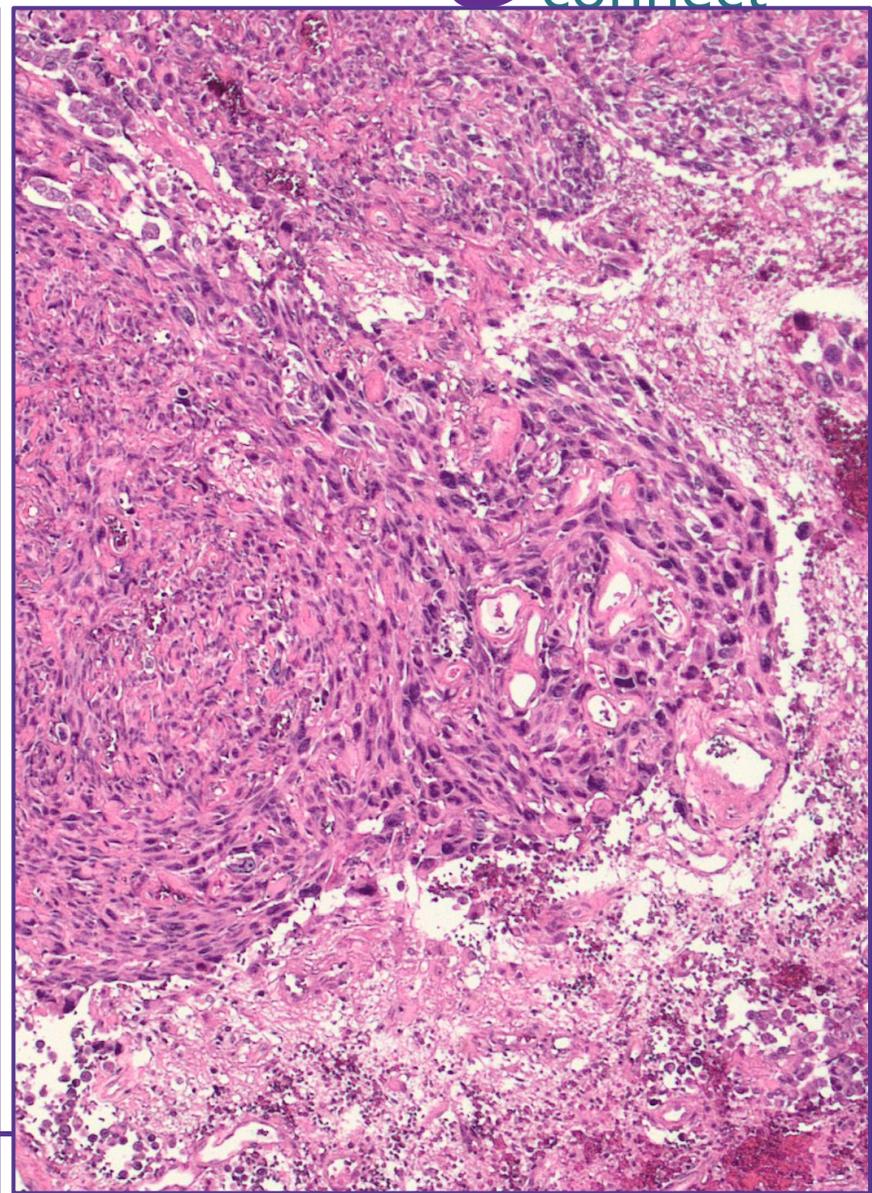
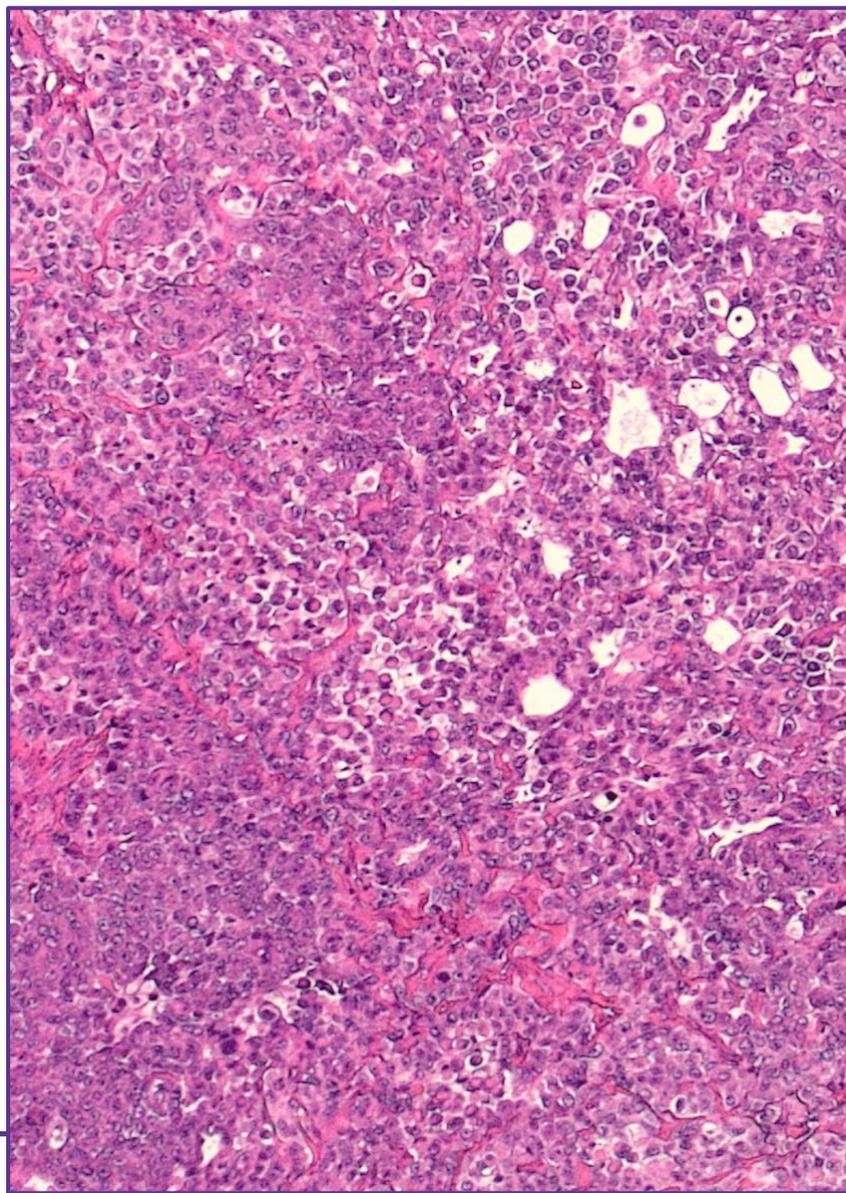
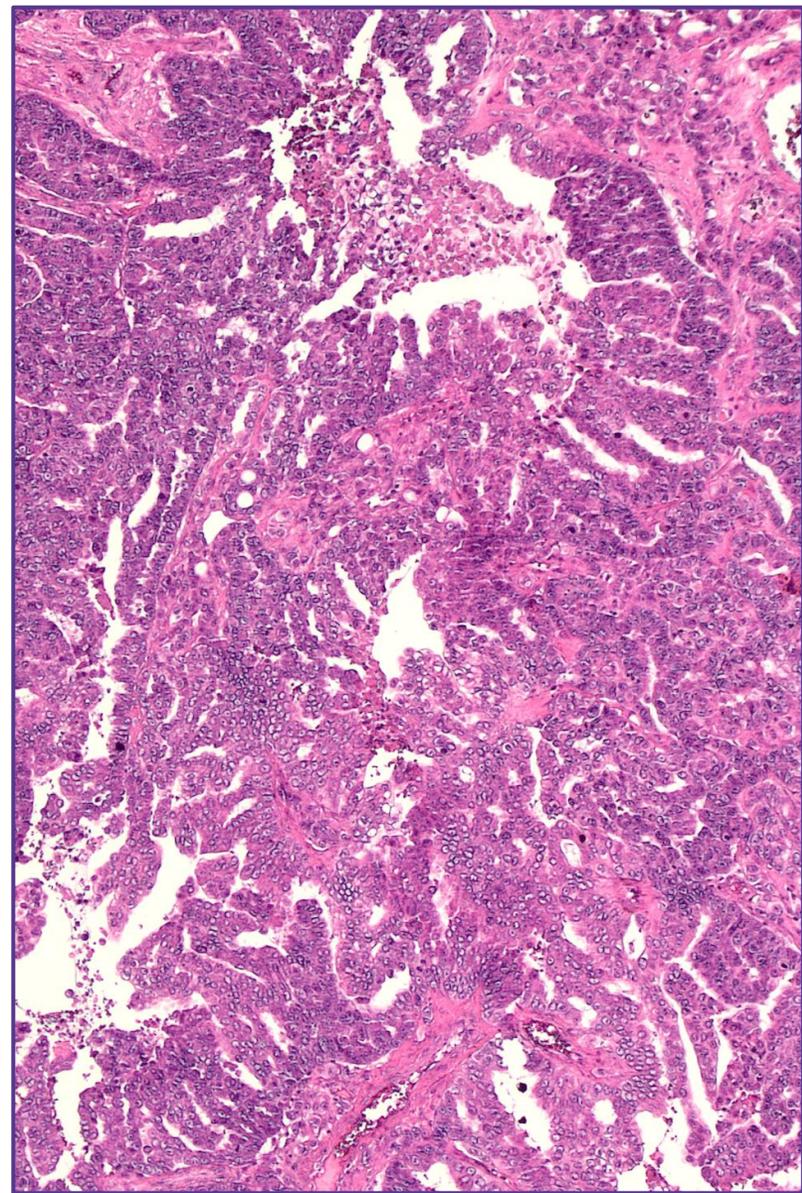
5.71% of fusion detection in tumors that are WT for canonical drivers, as defined by routine diagnostic testing of a small panel of genes



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Combined neoplasia => adenok with neuroendocrine & sarcomatoid features => BLASTOMA



# THANK YOU!



For further questions please  
contact:

[caterina.marchio@unito.it](mailto:caterina.marchio@unito.it)

# **TRK INHIBITOR THERAPY AND CASE STUDIES**

**David S. Hong MD**

**The University of Texas MD Anderson Cancer Center**

**Professor**

**Deputy Chairman in the Dept of Investigational Cancer Therapeutics (Phase I Program)**

**Clinical Medical Director of Clinical and Translational Research Center**

**Associate Vice President of Clinical Research**

# DISCLOSURES (LAST 36 MONTHS)

**Research(Inst)/Grant Funding (Inst):** AbbVie, Adaptimmune, Adlai-Nortye, Amgen, Astra-Zeneca, Bayer, Bristol-Myers Squibb, Daiichi-Sankyo, Deciphera, Eisai, Endeavor, Erasca, F. Hoffmann-La Roche, Fate Therapeutics, Genentech, Genmab, Ignyta, Infinity, Kite, Kyowa Kirin, Lilly, LOXO, Merck, Medimmune, Mirati, Mologen, Navier, NCI-CTEP, Novartis, Numab, Pfizer, Pyramid Bio, SeaGen, Takeda, TCR2, Teckro, Turning Point Therapeutics, VM Oncology

**Travel, Accommodations, Expenses:** Bayer, Genmab, AACR, ASCO, SITC, Telperian

**Consulting, Speaker or Advisory Role:** Adaptimmune, Alpha Insights, Acuta, Alkermes, Amgen, Aumbiosciences, Axiom, Baxter, Bayer, Boxer Capital, BridgeBio, COR2ed, COG, Cowen, Ecor1, Gennao Bio, Genentech, Gilead, GLG, Group H, Guidepoint, HCW Precision, Immunogen, Infinity, Janssen, Liberium, MedaCorp, Medscape, Numab, Oncologia Brasil, Pfizer, Pharma Intelligence, POET Congress, Prime Oncology, RAIN, Seattle Genetics, ST Cube, Takeda, Tavistock, Trieza Therapeutics, Turning Point, WebMD, YingLing Pharma, Ziopharm

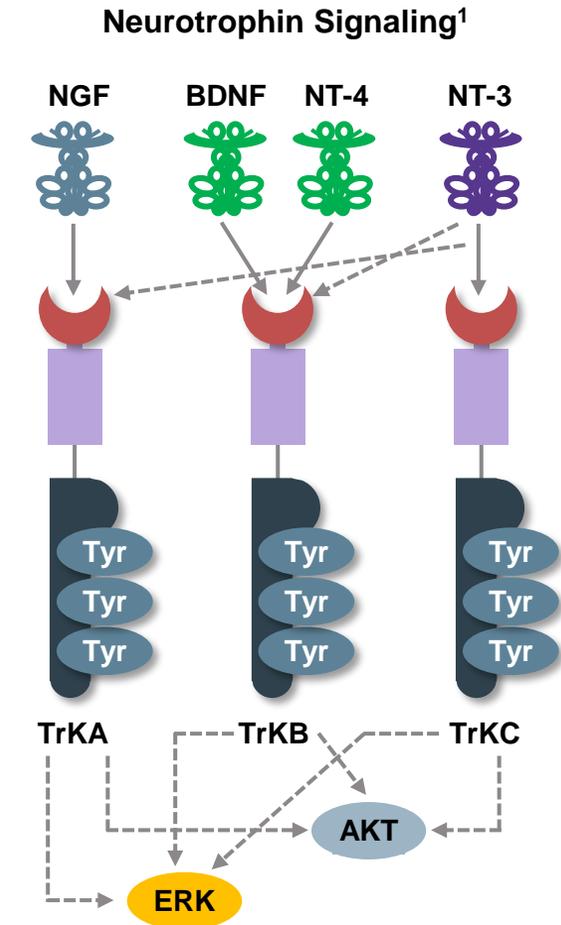
**Other ownership interests:** Molecular Match (Advisor), OncoResponse (Founder, Advisor), Telperian (Founder,Advisor)

# TRK RECEPTORS MEDIATE NEUROTROPHIN SIGNALING

- Neurotrophins are important growth factors that promote sympathetic nervous system development<sup>1,2</sup>
- Neurotrophin signaling occurs through activation of the tropomyosin-receptor kinase (TRK) receptor family<sup>1,2</sup>

Neurotrophin Family of Receptors<sup>1-5</sup>

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



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

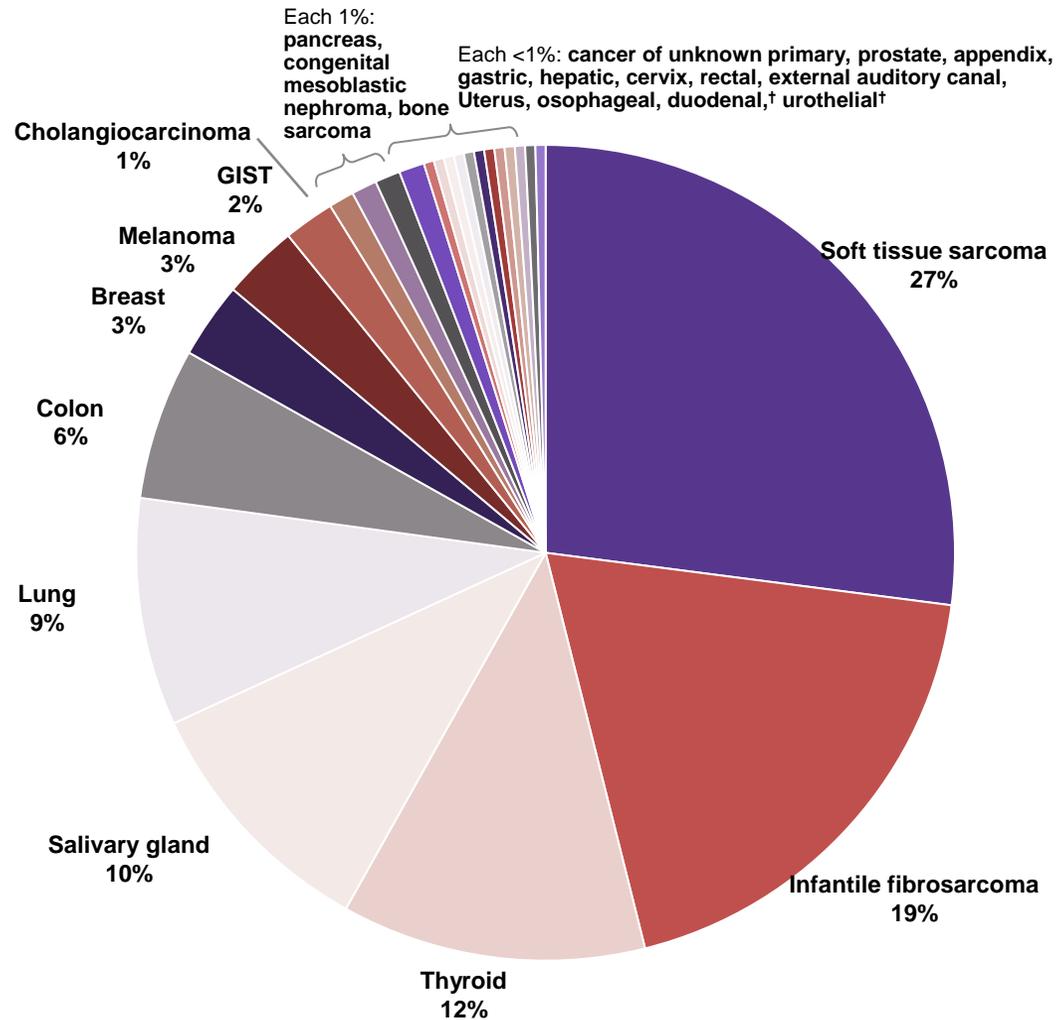
1. Nakagawara A. Cancer Letters. 2001;169:107-14; 2. Vaishnavi A, et al. Cancer Discov. 2015;5:25-34; 3. <https://www.ncbi.nlm.nih.gov/gene/4914>, accessed September 2, 2022; 4. <https://www.ncbi.nlm.nih.gov/gene/4915>, accessed September 2, 2022; 5. <https://www.ncbi.nlm.nih.gov/gene/4916>, accessed September 2, 2022

# APPROVED TRK INHIBITORS

## FIRST-GENERATION TRK INHIBITORS

	Larotrectinib	Entrectinib
<b>Drug targets</b>	TRKA/B/C	TRKA/B/C, ROS1, ALK
<b>ORR (all TRK fusion-positive cancers)</b>	81%	58%
<b>ORR (TRK fusion-positive lung cancers)</b>	71%	70%
<b>Median PFS (all TRK fusion-positive cancers)</b>	Not reached	11.2 months
<b>Dose reduction rate</b>	9%	27%

# BASELINE CHARACTERISTICS OF IRC-ASSESSED PATIENTS (N=244)



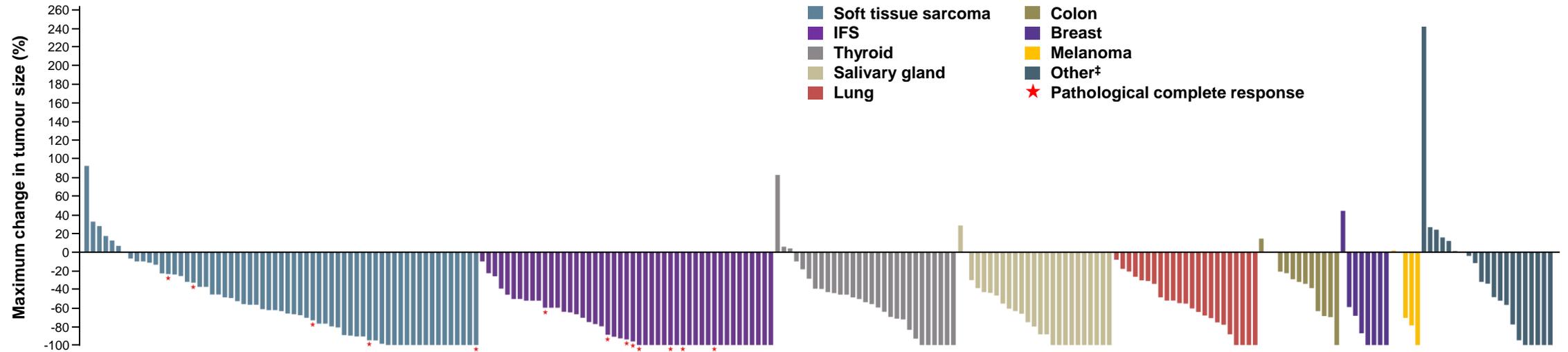
Characteristic	Integrated dataset (N=244)
<b>Sex, n (%)</b>	
Male	123 (50)
Female	121 (50)
<b>Age, median (range), years</b>	38 (0.1-84)
Paediatric (<18 years), n (%)	87 (36)
Adult (≥18 years), n (%)	157 (64)
<b>ECOG or equivalent Lansky PS, n (%)</b>	
0	126 (52)
1	87 (36)
2	25 (10)
3	6 (2)
<b>No. of prior systemic therapies, median range</b>	1 (0-10)
<b>No. of prior systemic regimens, n (%)</b>	
0	67 (27)
1	69 (28)
2	49 (20)
≥3	59 (24)
<b>NTRK gene fusion, n (%)</b>	
NTRK1	113 (46)
NTRK2	7 (3)
NTRK3	124 (51)

† Tumour types not presented in previous data cut.

ECOG, Eastern Cooperative Oncology Group; GIST, gastrointestinal stromal tumour; IRC; independent review committee; NTRK, neurotrophic tyrosine receptor kinase; PS, performance status

Drilon A. et al. ASCO 2022, Journal of Clinical Oncology 40, no. 16\_suppl:3100-3100.

# MAXIMUM CHANGE IN TARGET LESIONS (N=234<sup>†</sup>) AND BEST RESPONSE (N=244)

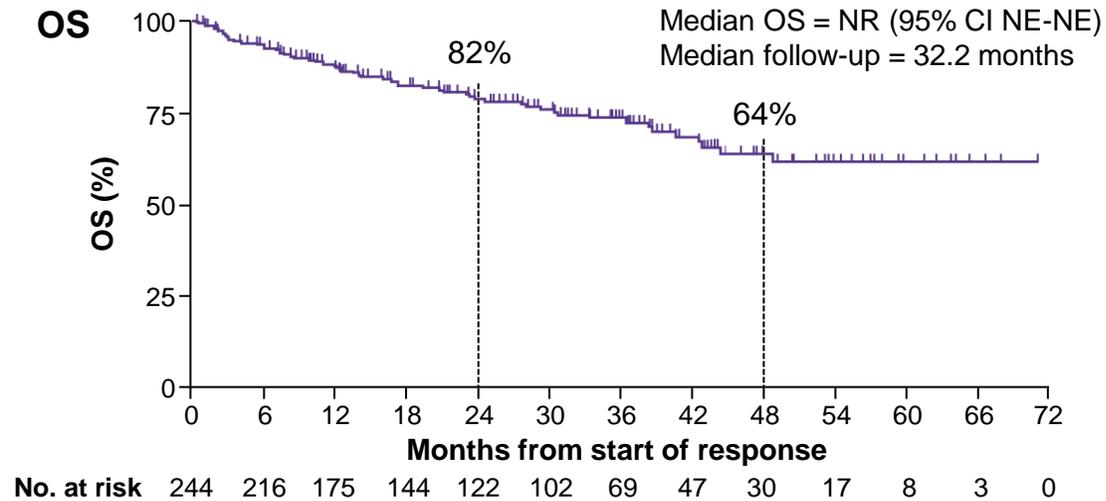
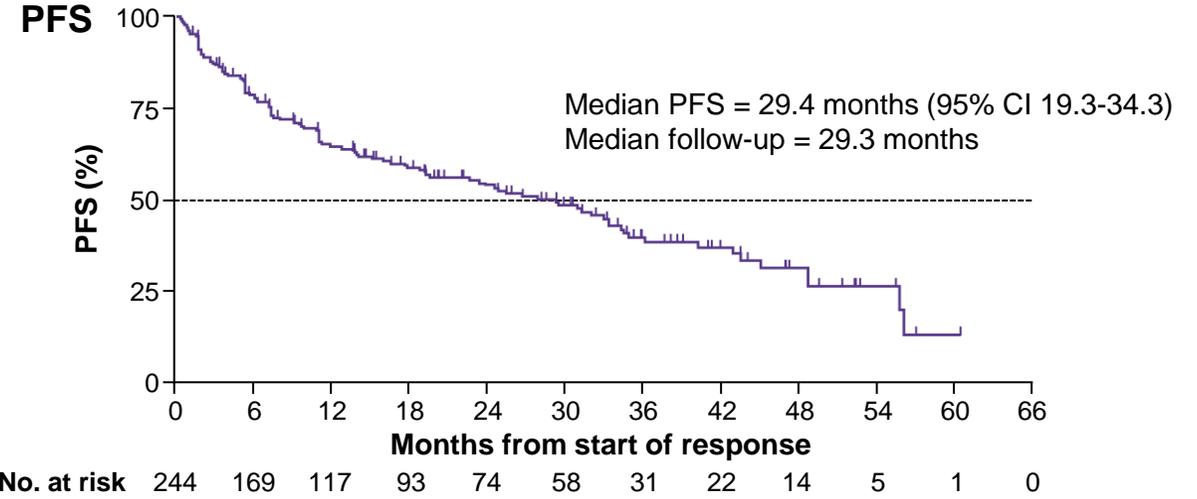
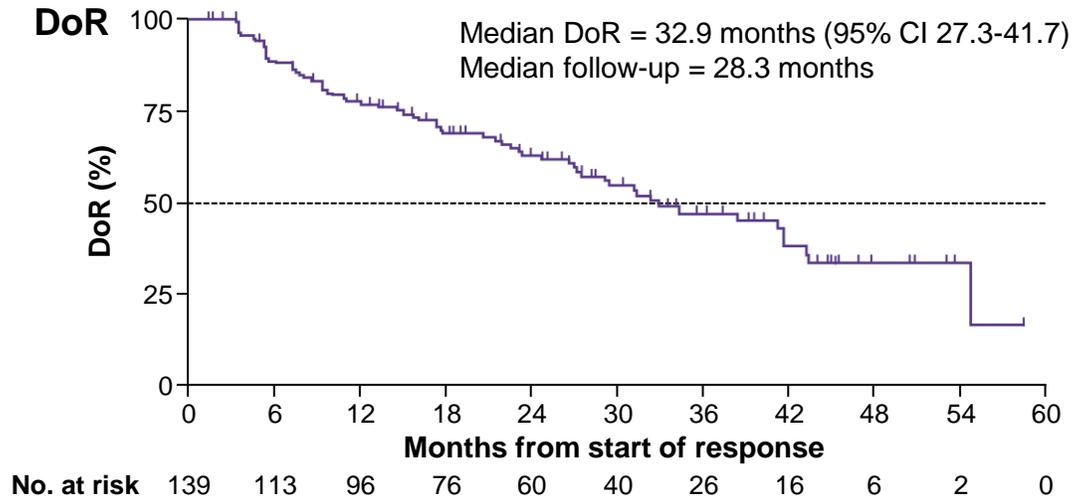


	Integrated dataset
<b>Evaluable patients, n</b>	244
<b>ORR, % (95% CI)</b>	69 (63-75)
<b>Best complete response, n (%)</b>	
Complete response	51 (21)
Pathological complete response	13 (5)
Partial response	104 (43)
Stable disease	41 (17)
Progressive disease	20 (8)
Not determined <sup>§</sup>	15 (6)

- Among 18 patients with known baseline CNS metastases evaluable per IRC, ORR was 83% (95% CI 59-96)
- The ORR for adult patients (n=157) was 64% (95% CI 56-72). Median DoR was 41.7 months (95% CI 32.5-NE) at a median follow-up of 28.5 months

<sup>†</sup> Ten patients had no measurable lesions assessed by IRC; <sup>‡</sup> Other includes appendix (n=1), bone sarcoma (n=2), cancer of unknown primary (n=1), cervix (n=1), cholangiocarcinoma (n=2), congenital mesoblastic nephroma (n=2), duodenal (n=1), esophageal (n=1), external auditory canal (n=1), GIST (n=4), pancreas (n=2), prostate (n=1), rectal (n=1), urothelial (n=1). <sup>§</sup> Patients who discontinued study drug without evaluable postbaseline assessments.

# DoR, PFS AND OS



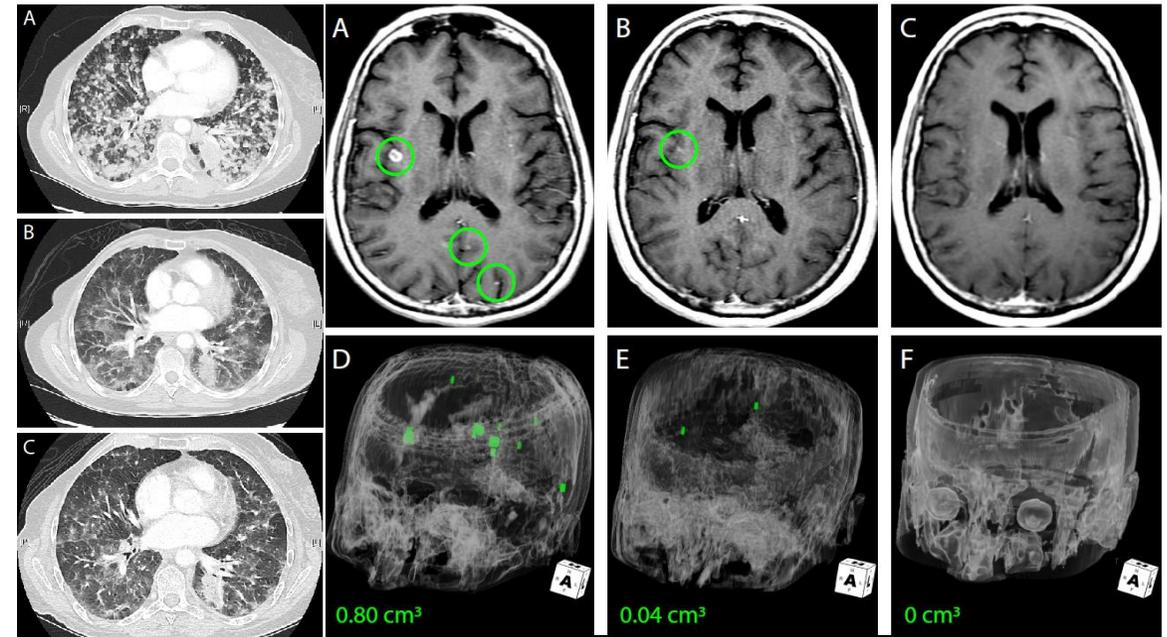
# CASE 1: TREATMENT-NAÏVE *EPS15-NTRK1*-POSITIVE LUNG ADENOCARCINOMA WITH INTRACRANIAL AND EXTRACRANIAL RESPONSE TO LAROTRECTINIB

76-year-old woman with lung adenocarcinoma

- Metastatic to lung and brain
- No prior systemic therapy, surgery or radiotherapy
- Refused platinum doublet therapy

**Treated with larotrectinib**

- Confirmed PR (−34%)
- Near intracranial CR (−95%, volumetric)
- Remains on therapy at 6+ months



Patient was not evaluable at data cut-off.

CR, complete response; *EPS15*, Epidermal growth factor receptor substrate 15; *NTRK*, neurotrophic tyrosine receptor kinase; PR, partial response

Rosen, et al. JCO Precision Oncology (In press)

Drilon A, et al. J Clin Oncol. 37, 2019 (suppl; abstr 2006)

# CASE 2: *TPM3-NTRK1* FUSION MSI HIGH CRC

## Patient

- 85-year-old female who presented with a presented with obstructive symptoms
- Noted to have metastatic disease to the bowel and liver

## Prior Treatment

- Tumor sample disclosed dMMR (*MLH1/PMS2*), *TPM3-NTRK1* fusion, CIMP high
- Received pembrolizumab (7/2018-9/2018) with no response and progressive disease

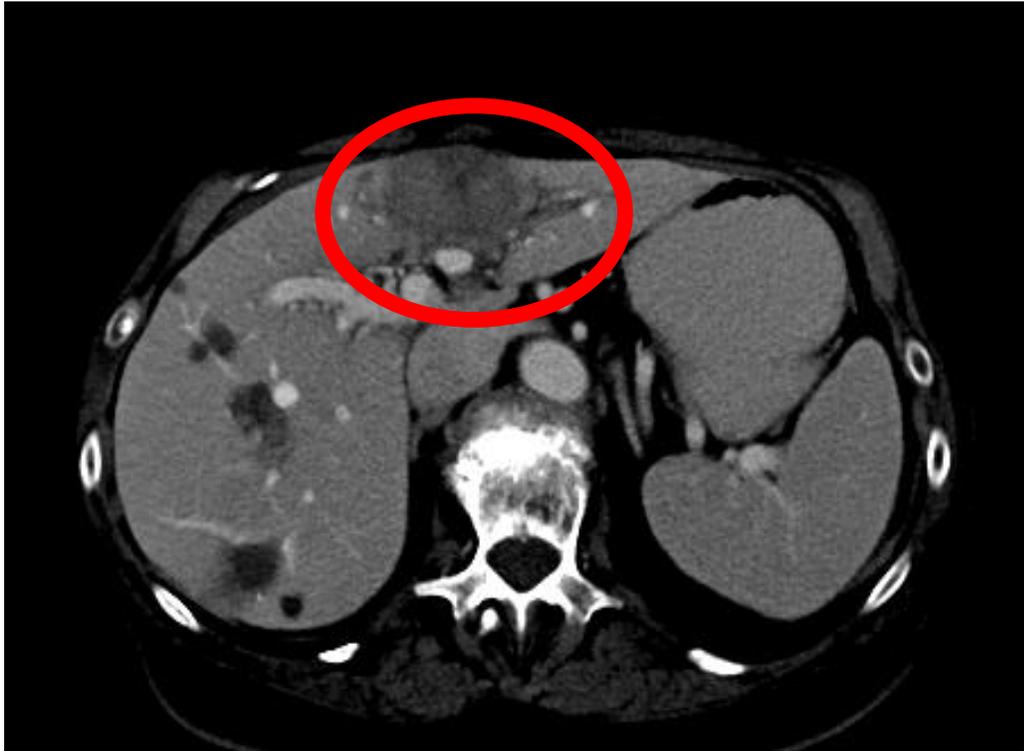
## Larotrectinib Treatment

- Subsequently enrolled to the phase 2 larotrectinib trial (10/2018), NAVIGATE, at 100mg BID orally. Patient developed grade 3 LFTs dose reduced to 50 mg BID

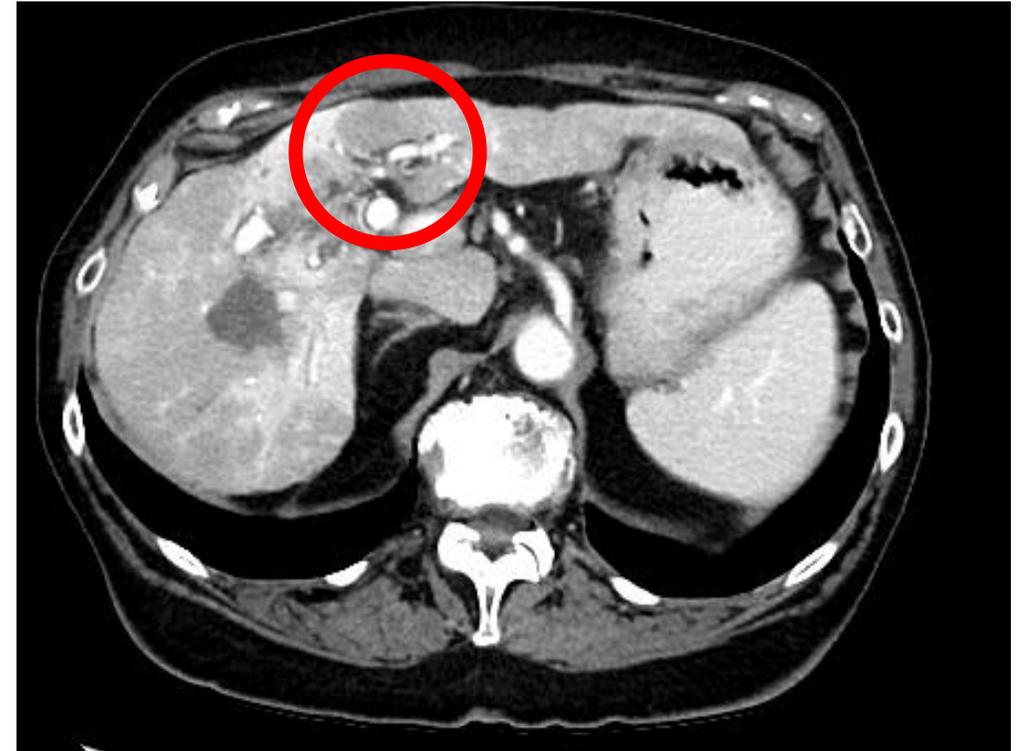
## Outcomes

- Confirmed PR of (-42%) and remains on larotrectinib (8/2022)

## CASE 2: *TPM3-NTRK1* FUSION MSI HIGH CRC



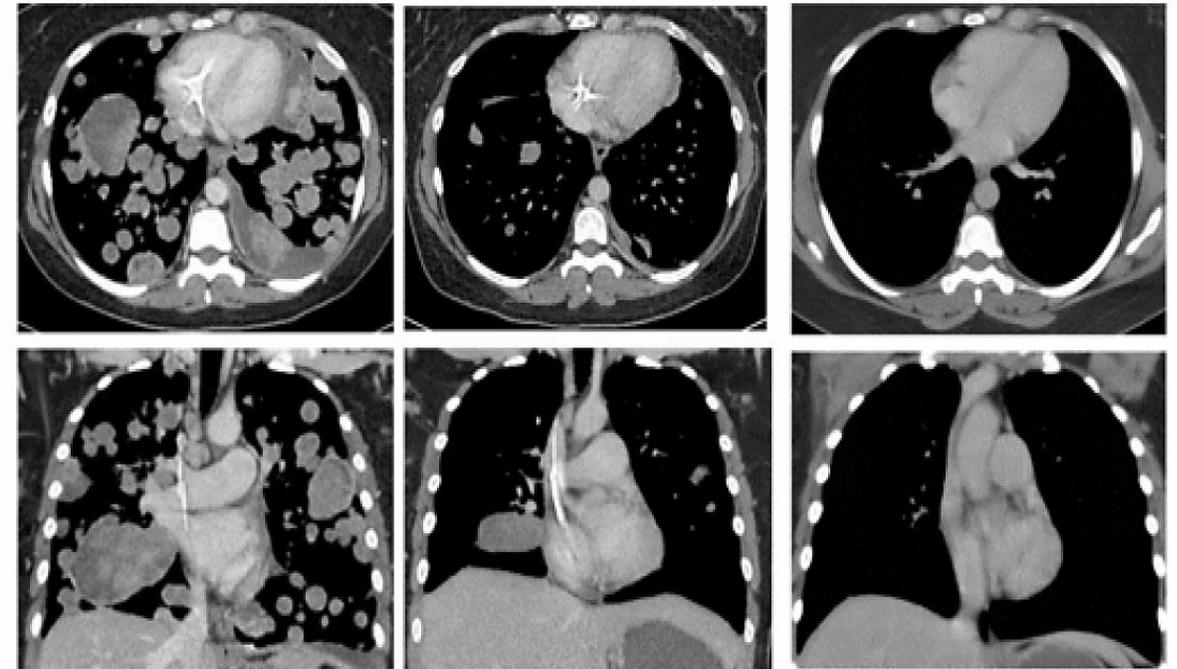
**Study baseline**



**End of cycle 4**

# CASE 3: LMNA–NTRK1 FUSION SOFT TISSUE SARCOMA

- 42-year-old female with undifferentiated sarcoma progressed through epirubicin, ifosfamide, sorafenib, and doxorubicin
- 100 mg BID
- Rapid resolution of dyspnea and hypoxemia
- Confirmed partial response



Study baseline

Study cycle 3 day 1

Study cycle 13 day 1

PP-VIT-ALL-0137-2  
PP-VIT-ES-0059-1 09/2019

BID, twice a day; LMNA, Pre-lamin A/C; NTRK, neurotrophic tyrosine receptor kinase

# THANK YOU ALL!



# ACKNOWLEDGEMENTS



We thank the patients and their caregivers for taking part in our trials



For further questions please contact:  
[dshong@mdanderson.org](mailto:dshong@mdanderson.org)

# **SUCCESSFUL *NTRK* FUSION INHIBITION**

**Philipp Ivanyi**

**Adjunct Professor, MD, Assistant Medical Director**

**Head and Neck-, GU, Sarkoma-center**

**Comprehensive Cancer Center, Lower Saxony**

**Department of Hematology, Hemostasis, Oncology and Stem-cell**

**Transplantation**

**Hannover Medical School, Germany**

# DISCLOSURES

## **Advisory Fees, Expert Testimony**

BMS, Bayer, ClinSol, Deciphera, Eisai, EMD-Serono, EUSA, H5-Oncology, Ipsen, Merck Serono (Global), Metaplan, MSD, Onkowissen, Pfizer, Roche

## **Lecture Honoraria**

AIM, Apogepha, AstraZeneca, Astella, BMS, Bayer (+Europe, Global), Deciphera, DKG-Onkoweb, Eisai, EUSA, FoFM, Id-Institut, Ipsen (Europe), Merck Serono (+Europe, Global), MSD, MedKom, MTE-Academy, MedWiss, New Concept Oncology, Onkowissen-tv.de, Pharma Mare, Pfizer, Roche, ThinkWired!, Schmitz-Kommunikation, StreamedUP!, Solution Academy, Vivantis

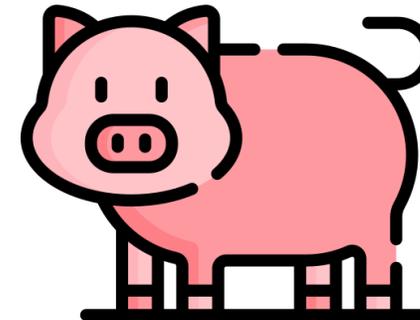
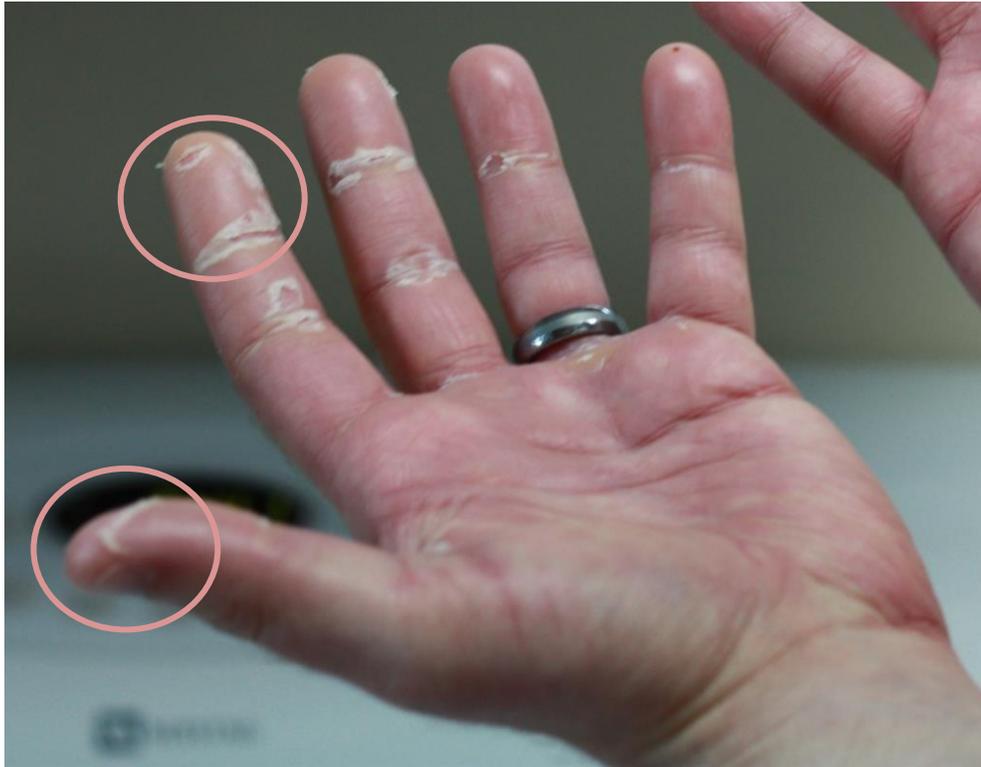
## **Clinical Trials/Research Grants**

AIO, AstraZeneca, BMS, Bayer, GSK, Ipsen, Lilly, Merck Serono, Niedersächsische Krebsgesellschaft, Novartis, EUSA, Eisai, Pfizer, MSD, Roche, Stiftung Immunonkologie, Wilhelm Sander Stiftung

## **Travel grants, Others**

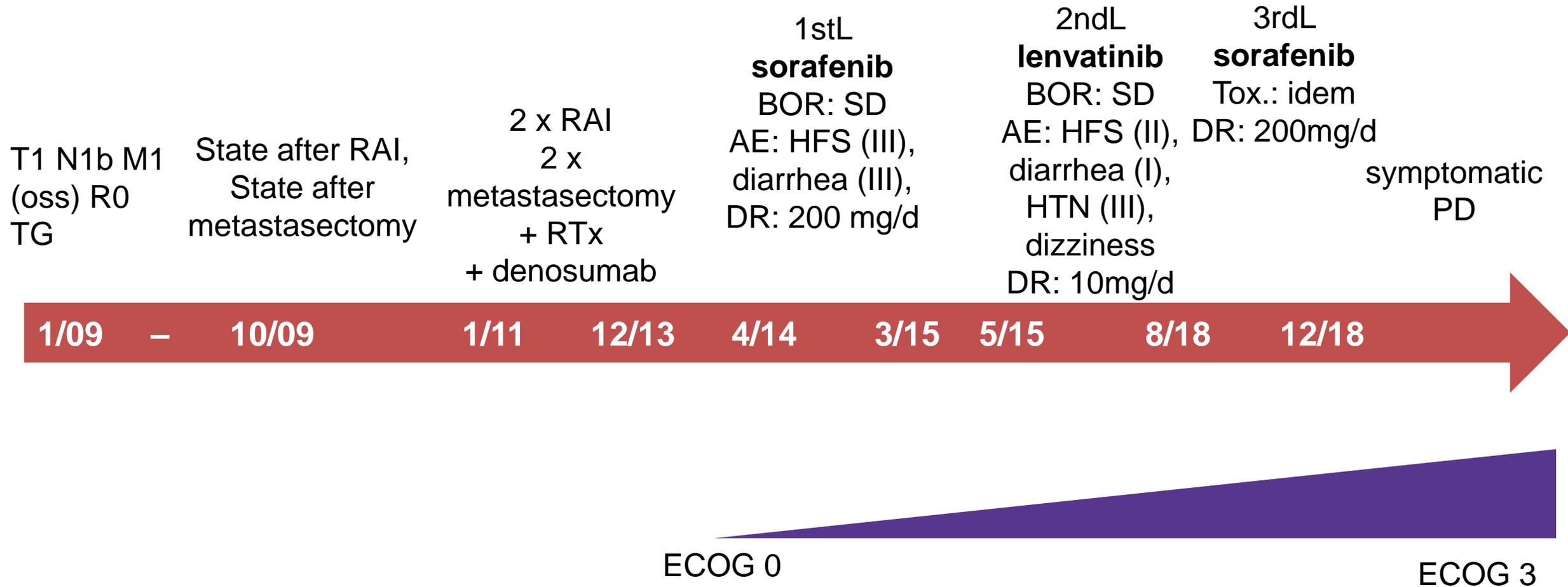
BB-Biotech, BMS, Bayer, Deutsche Gesellschaft für Thoraxchirurgie, EUSA, Ipsen, Novartis, Merck, Pharma Mare

**04/2010**  
**56 YEAR**  
**DR. MED. VET**



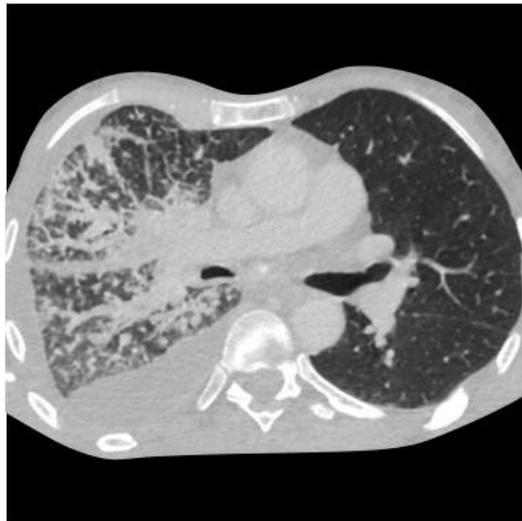
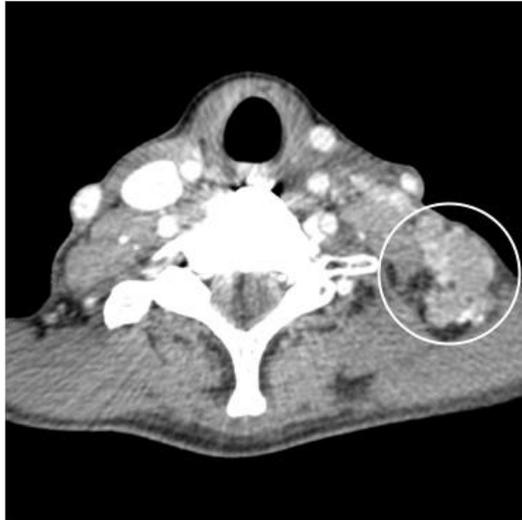
**04/2010**  
**56 YEAR**  
**DR. MED. VET**  
**TGC**

# FICTIONAL PATIENT CASE



AE, adverse event; BOR, best overall response; DR, dose reduction; ECOG, Eastern Cooperative Oncology Group; HFS, hand-foot syndrome; HTN, hypertension; PD; disease progression; RAI, radioactive-iodine; RTx, radiotherapy; SD, stable disease

1/2019

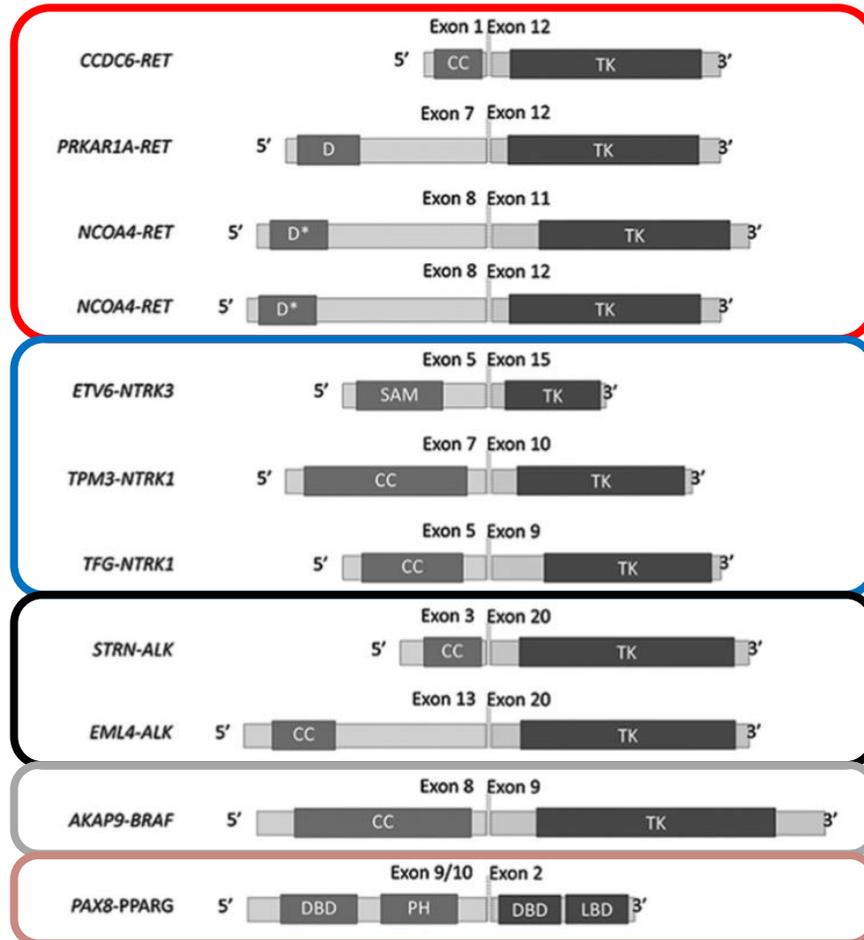


baseline

- Sorafenib, TBP
- Lenvatinib
- Trial/off-label?
- BSC



**56 YEAR  
DR. MED. VET  
TGC  
12/18  
END OF OPTIONS –  
HOPE IN *NTRK* INHIBITION?**



*RET*

*NTRK*

*ALK*

*BRAF*

*PPARG*

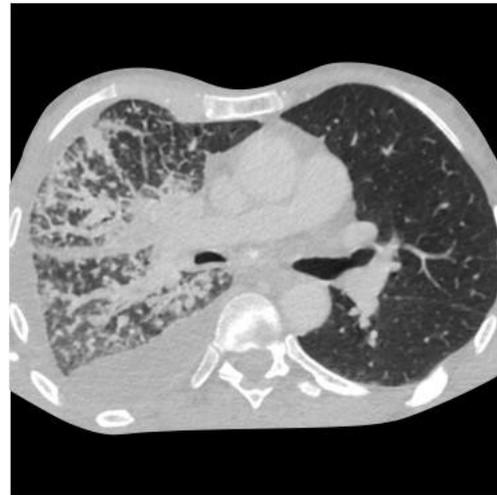
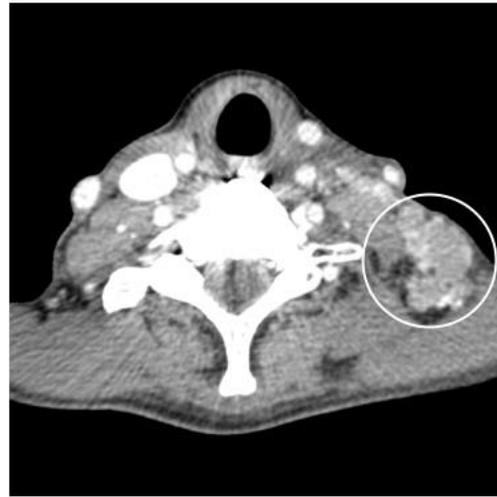
5-25% of PTC are observed to harbour TRK fusions<sup>2</sup>

**END OF OPTIONS –  
*NTRK*, REASONABLE IN TGC?**

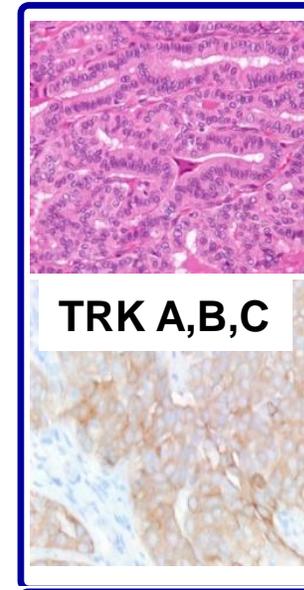


**@ pathologist of my confidence**

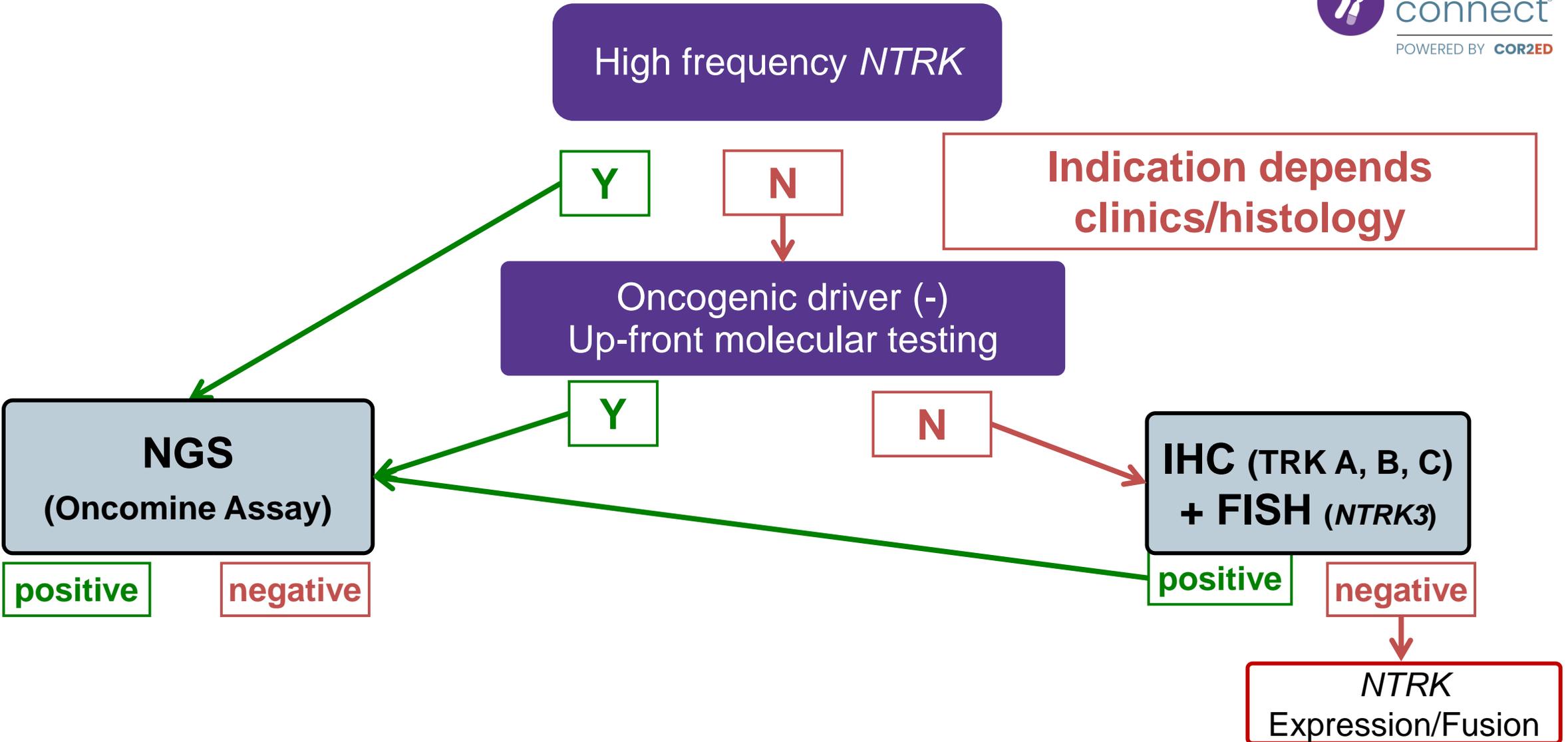
1/2019



baseline

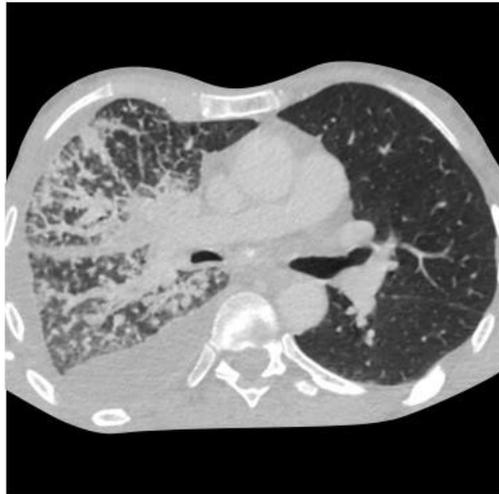
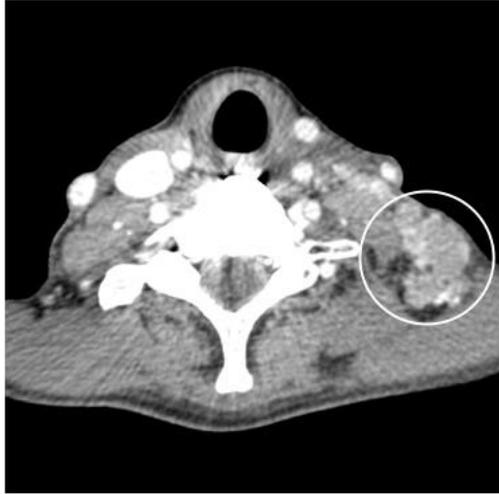


# ***NTRK*, MHH – STRATEGY (2022)**

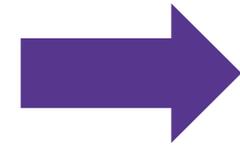
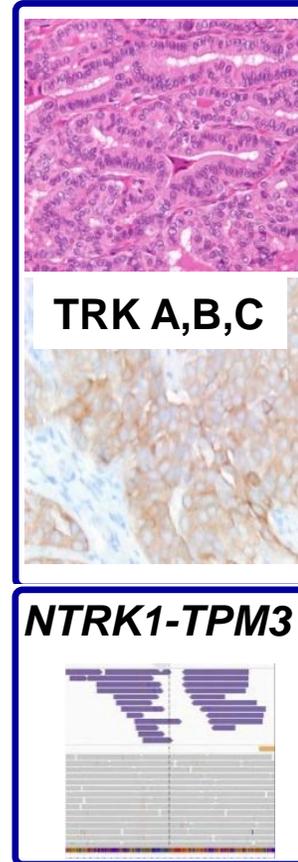


**HE WHO SEEKS – FINDS!**

1/2019



baseline



Starting  
NTRKi  
(Larotrectinib)



Fictional case, MHH

ALT, alanine transaminase; BW, body weight; CEA, carcinoembryonic antigen; CR, complete response; ECOG, Eastern Cooperative Oncology Group; HB, haemoglobin; ORR, objective response rate; PR, partial response

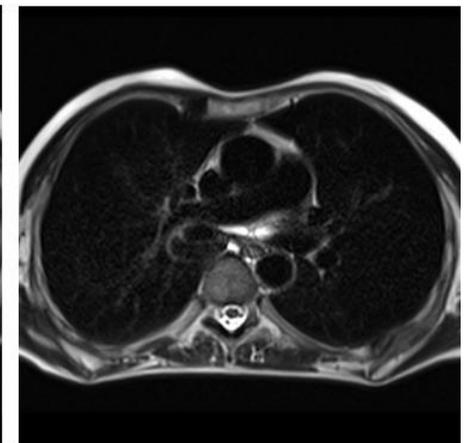
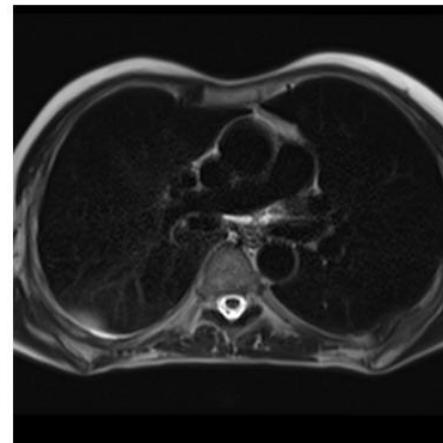
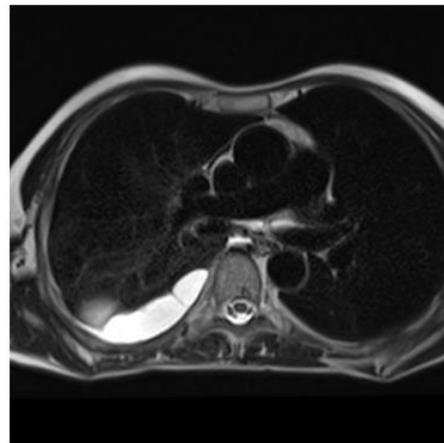
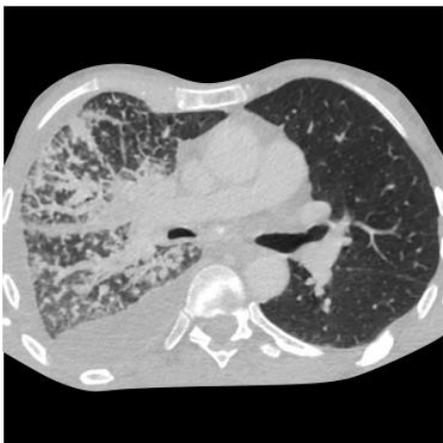
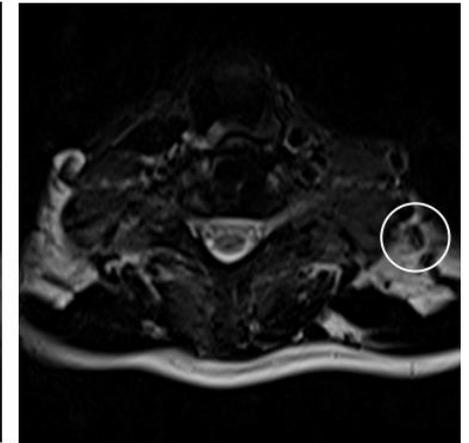
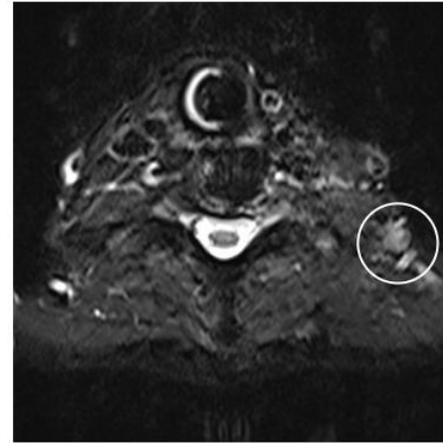
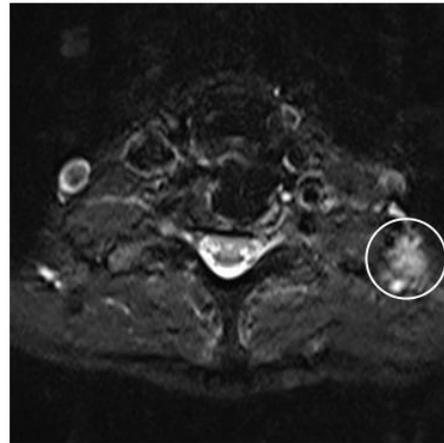
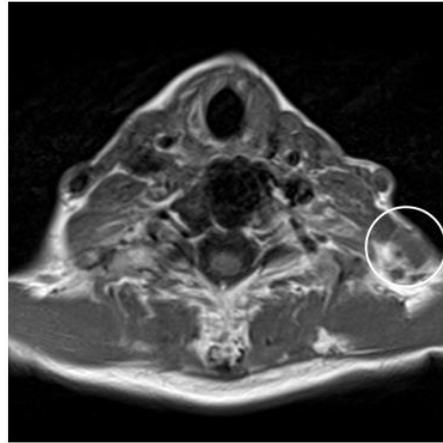
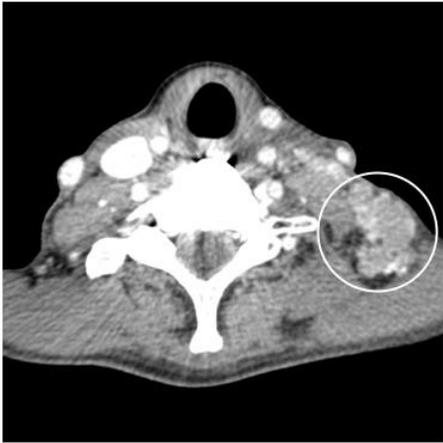
1/2019

3/2019

5/2019

7/2019

9/2019



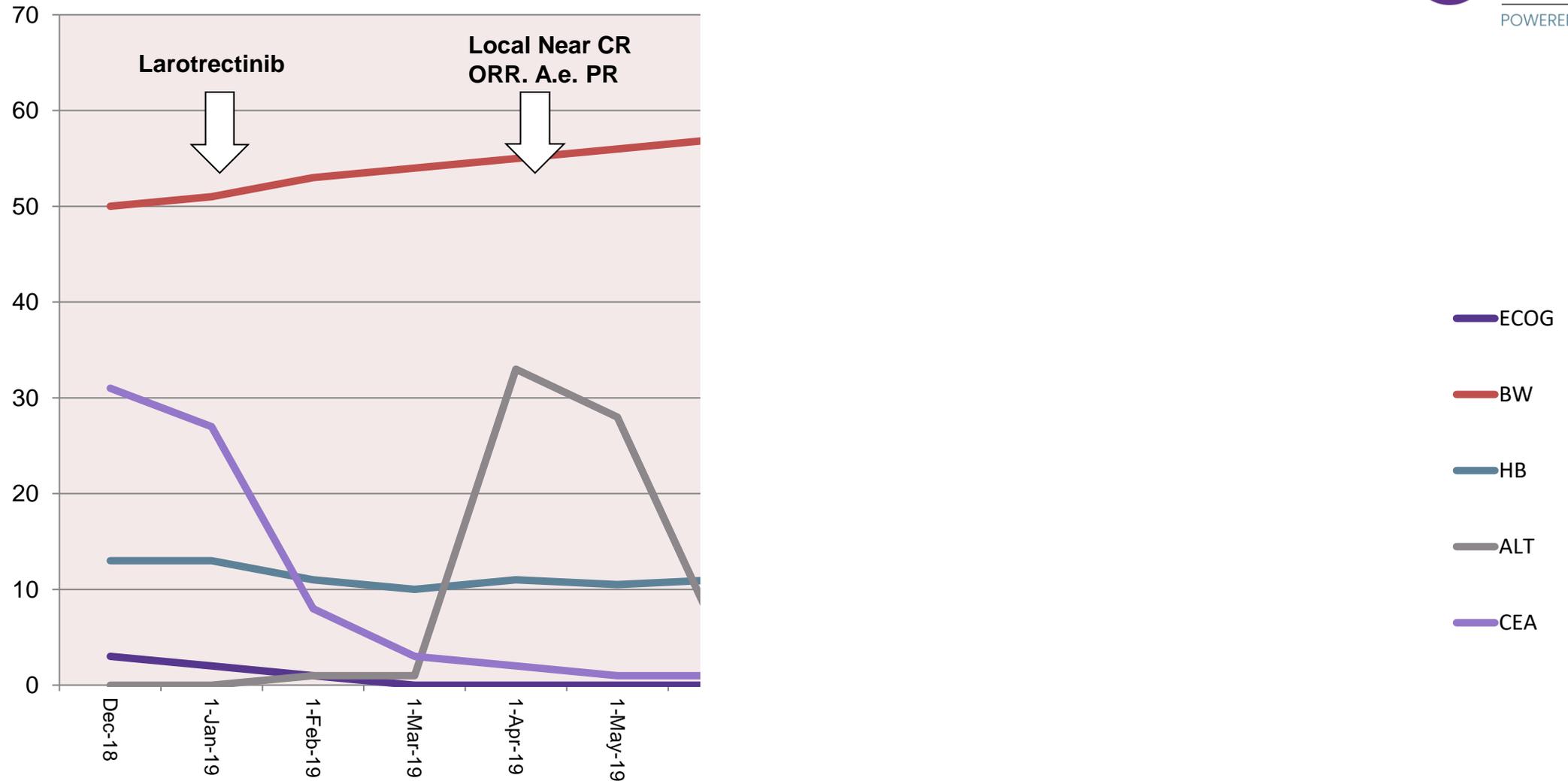
baseline

PR

PR

CR

CR

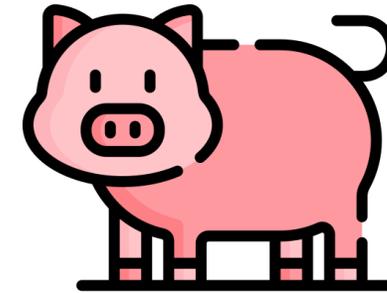


Fictional case, MHH

ALT, alanine transaminase; BW, body weight; CEA, carcinoembryonic antigen; CR, complete response; ECOG, Eastern Cooperative Oncology Group; HB, haemoglobin; ORR, objective response rate; PR; partial response

# CONCLUSIONS

- He who seeks finds!
- However, rare alteration
- NTRKi in *NTRK*-fusion tumours:
  - highly potent
  - highly efficient
  - safe



**Thanks for your attention – [Ivanyi.philipp@mh-hannover.de](mailto:Ivanyi.philipp@mh-hannover.de)**

# QUESTIONS FROM PRE-MEETING SURVEY

## TESTING

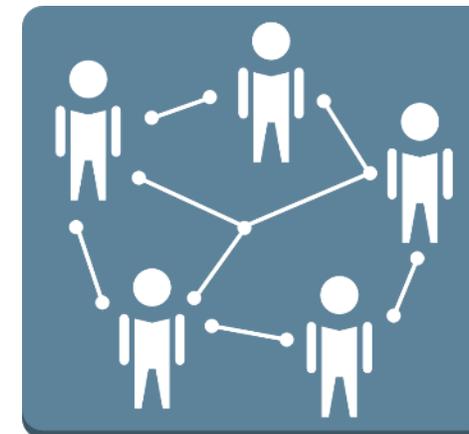
1. Should we test our patients for NTRK after the failure of first line therapy?
2. Is NTRK status changing during different lines of therapies?

## EFFICACY

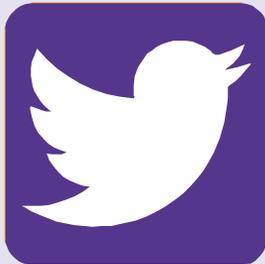
3. What about the second line efficacy of NTRKi in NTRK(+) tumours?
  4. Is there any experience in combining NTRK inhibitors with immune checkpoint inhibitors?
  5. Are there data on melanoma and other skin cancers?
-

# THANK YOU!

- **Thank you** for your participation and input during this meeting, slides will be made available for download.
- Please complete the short **post-meeting survey** via COR2ED ENGAGE, your feedback is important to us
- **Honorarium forms** can be accessed and submitted via the COR2ED Engage



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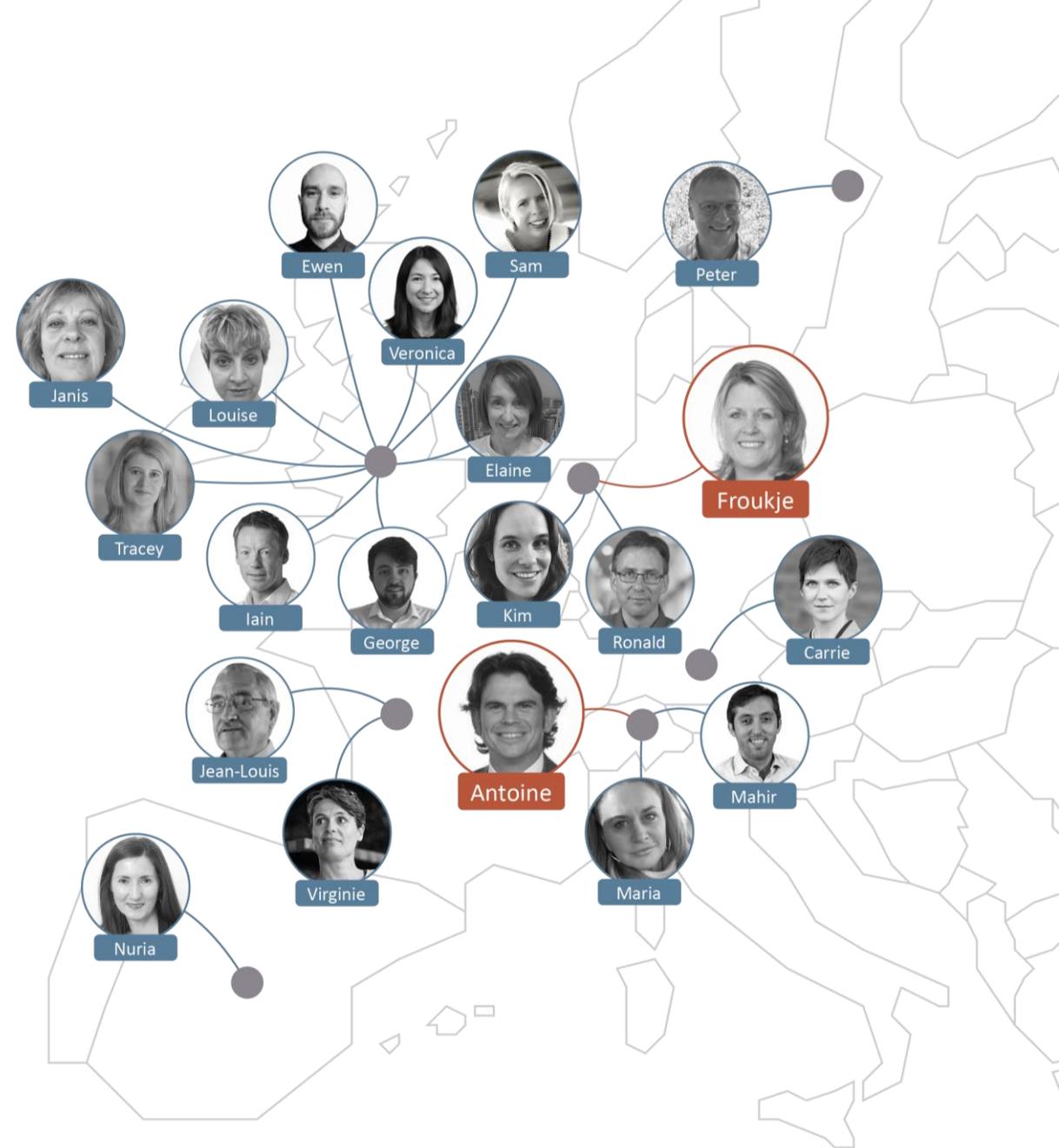
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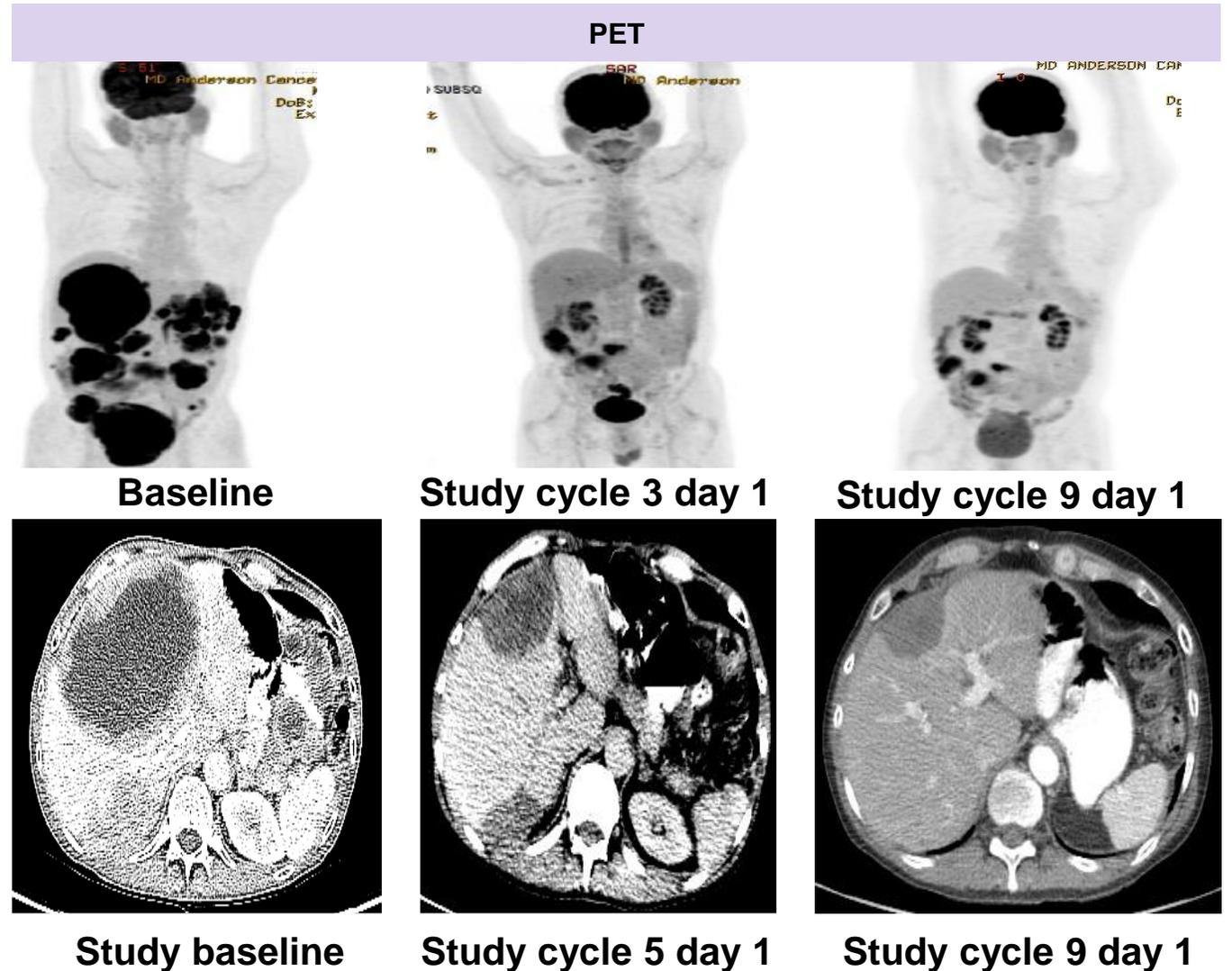


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# APPENDIX

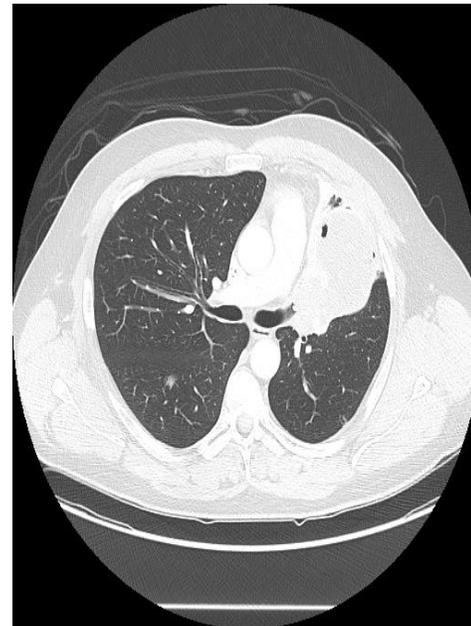
# ETV6-NTRK3 FUSION GIST

- 55 yo male with GIST progressed through imatinib, sunitinib, sorafenib, nilotinib, and regorafenib
- 150 mg BID
- Confirmed partial response

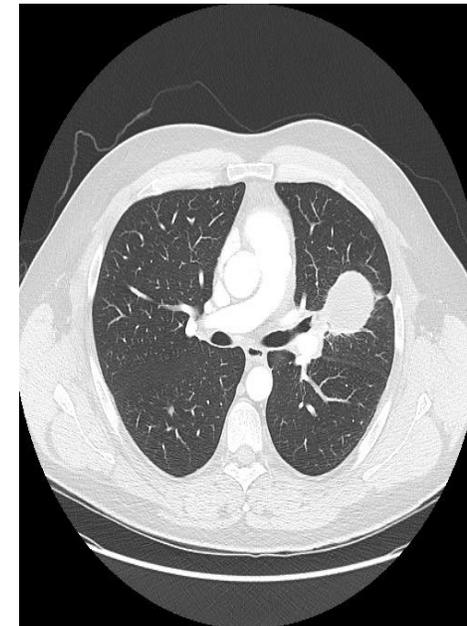


# ETV6-NTRK3 FUSION MAMMARY ANALOGUE SECRETORY CARCINOMA OF THE SALIVARY GLAND (MASC)

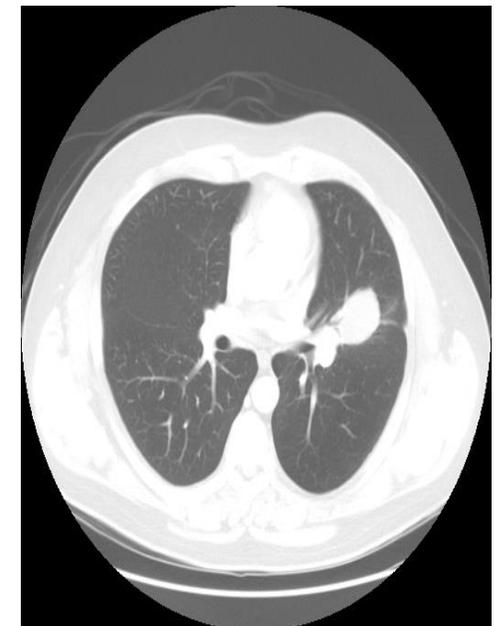
- 33 yo male progressed through docetaxel, carboplatin and 5FU
- 100 mg BID
- Confirmed partial response



**Study baseline**



**Study cycle 3 day 1**



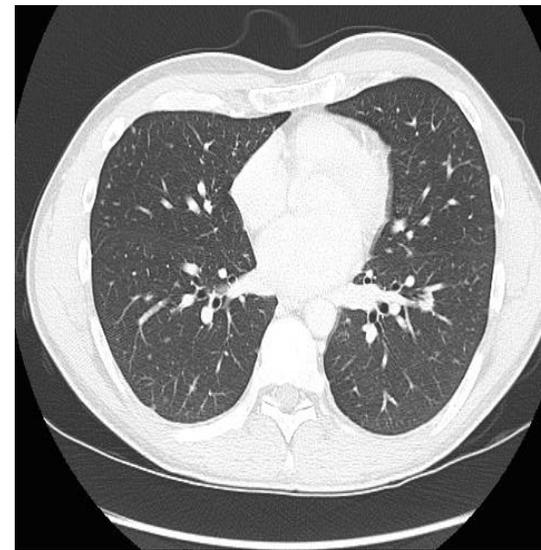
**Study cycle 9 day 1**

# ETV6-NTRK3 FUSION PAPILLARY THYROID CANCER

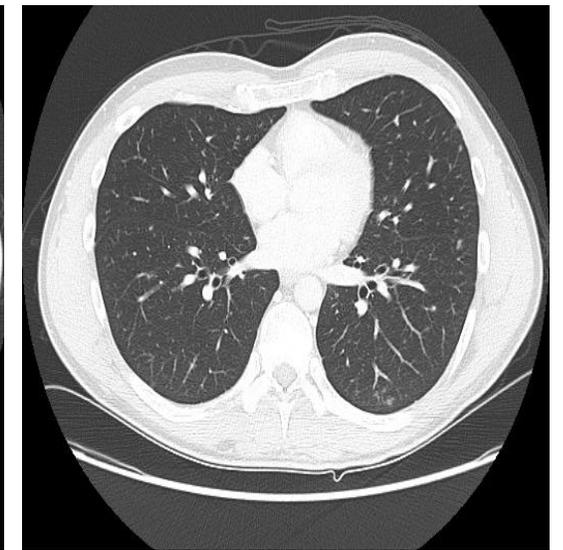
- 33 yo male progressed through RAI, pazopanib, trametanib
- 100 mg BID
- Confirmed partial response
- Rapid improvement cervical lymphadenopathy



**Study baseline**



**Study cycle 3 day 1**



**Study cycle 7 day 1**