Lung Cancer Clinical Cases on *RET & NTRK*

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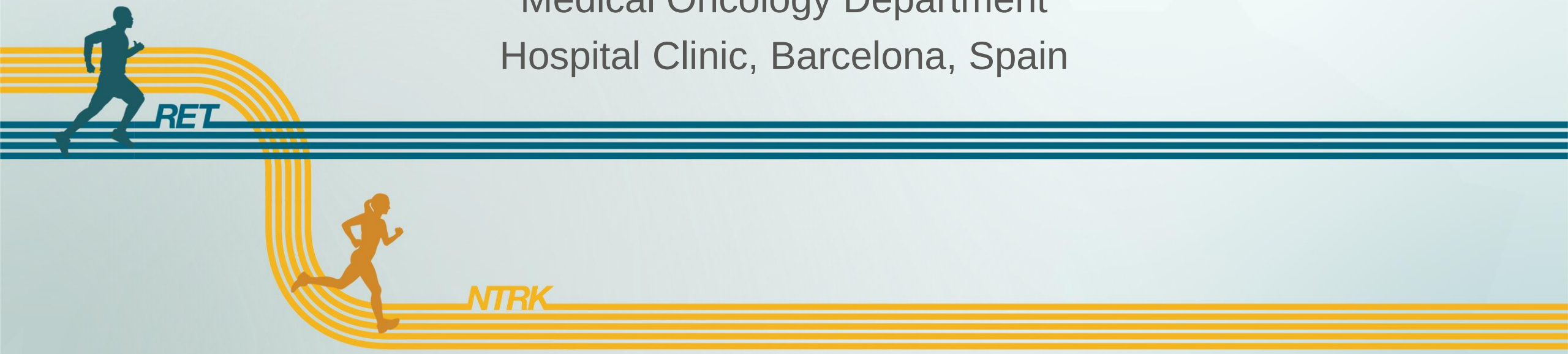

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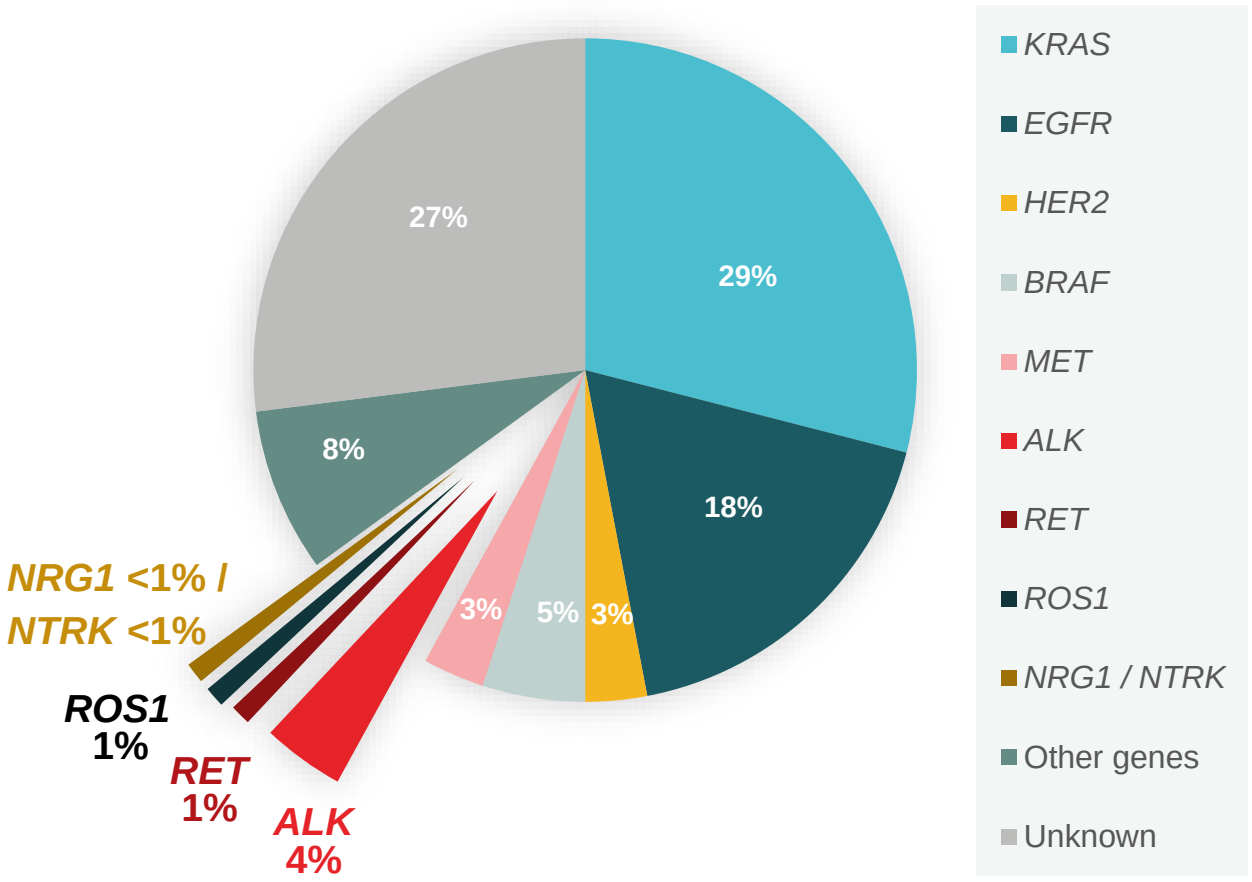
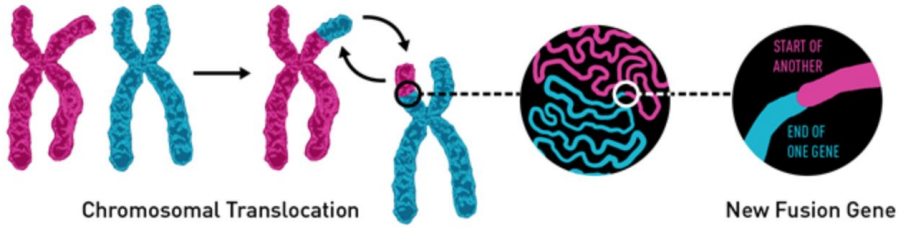
Oncogenic Drivers and Gene Fusions in NSCLC



Original figure N. Reguart. Adapted from Chevallier M, et al. World J Clin Oncol 2021;12:217–37

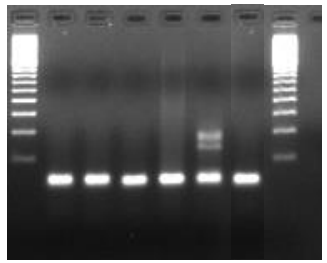


- Oncogenic drivers are common in NSCLC, especially in adenocarcinoma[1]
- **Gene fusions make up about 6%** of all oncogenic drivers in NSCLC[1]
- Outcomes for patients with actionable drivers are improved when receiving targeted therapies[2]
- Identifying these patients at diagnosis is a challenge that requires **multidisciplinary team efforts**

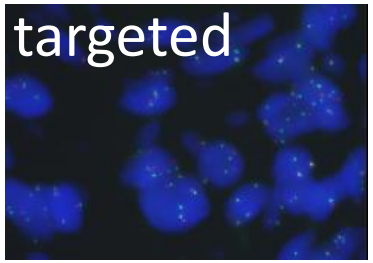
1. Chevallier M, et al. *World J Clin Oncol* 2021;12:217–37; 2. Tan L, et al. *Intern Med J* 2018;48:37–44.

Testing for Gene Fusions: *ALK, ROS1, RET, NTRK, NRG1*

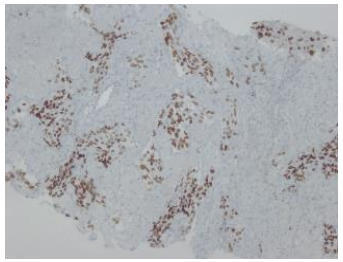
Specific targeted



PCR



FISH



IHC

Multiplex

NGS testing

TECHNIQUES	GENE
Fluorescent *in-situ* hybridization (FISH)	*ALK, ROS1, RET, NTRK*
Immunohistochemistry (IHC)	*ALK, ROS1*, NTRK**
Reverse transcription polymerase chain reaction (RT-PCR)	*ALK, ROS1, RET, NTRK*
Next Generation Sequencing (NGS)**	*ALK, ROS1, RET, NTRK, NRG1*

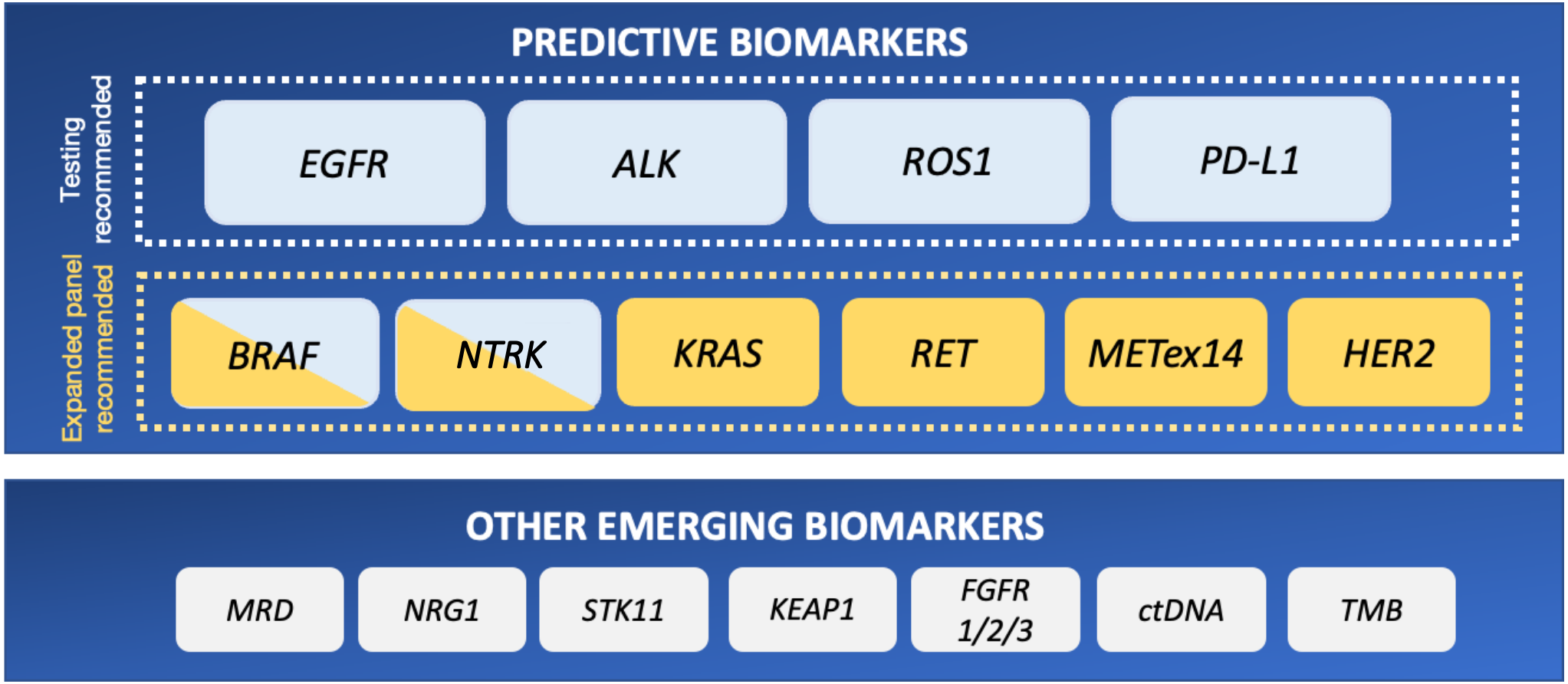
* Positive IHC results should be confirmed by an orthogonal method – FISH or RNA-NGS

**RNA-NGS testing preferred

1. Planchard D, et al. *Ann Oncol* 2018;29(Suppl 4):iv192–iv237. Updated version 2020, available at https://www.esmo.org/content/download/347819/6934778/1/ESMO-CPG-mNSCLC-15SEPT2020.pdf (Accessed August 2022);
2. Kerr KM, et al. *Lung Cancer* 2021;154:161–75.

The Evolving Landscape of Biomarker Testing in NSCLC

ESMO, NCCN, ASCO, CAP/IASLC/AMP guidelines



Original figure N. Reguart. Adapted from Kerr KM, et al. *Lung Cancer* 2021;154:161–75.

Implementation of Broader Molecular Testing

ESMO Scale of Clinical Actionability for molecular Targets (ESCAT)

Gene	Genetic Alteration	ESCAT
	TIER EVIDENCE I	
EGFR	Common mutations (Del19, L858R)	IA
	Acquired T790M exon 20	IA
	Uncommon (G719X exon 18, L861Q exon 21, S768I exon 20)	IB
ALK	Fusions (mutations as mechanism of resistance)	IA
MET	Mutations ex 14 skipping	IB
BRAF^{V600}	Mutations	IB
ROS1	Fusions (mutations as mechanism of resistance)	IB
NTRK	Fusions	IC
RET	Fusions	IC
	TIER EVIDENCE II-III	
KRAS^{G12C}	Mutations	IIB
EGFR	Exon 20 insertion	IIB
ERBB2	Hotspot mutations and Amplifications	IIB
MET	Focal amplifications (acquired resistance on EGFR TKI)	IIB
BRCA 1/2	Mutations	IIIA
PIK3CA	Hotspot mutations	IIIA
NRG1	Fusions	IIIB

ESMO Recommendations for the use of NGS in Lung Cancer

- NSCLC is among the solid tumours with the **highest number of ESCAT tier I** alterations[1]
- In non-squamous NSCLC, it is recommended that a tumour (or plasma) sample is profiled using **NGS technology**, in order to detect all tier **I** alterations[2]
- Larger NGS multigene panels could be used if they add acceptable extra cost compared with small panels[2]
- Considering the high frequency of fusions, **RNA-based NGS, or DNA-based NGS** designed to capture such fusions, are the preferred options[2]

1. Mateo J, et al. *Ann Oncol* 2018;29:1895–902; 2. Mosele F, et al. *Ann Oncol* 2020;31:1491–505.

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Clinical Case #1

Patient History

- Female, 76-year-old, nun
- **Never smoker**
- Medical history: severe osteoporosis and multiple vertebral fractures
- Drug history: bisphosphonates, supplements of calcium and vitamin D, pantoprazole, paracetamol occasionally
- In July 2018, a CT scan is requested by the GP due to persistent cough

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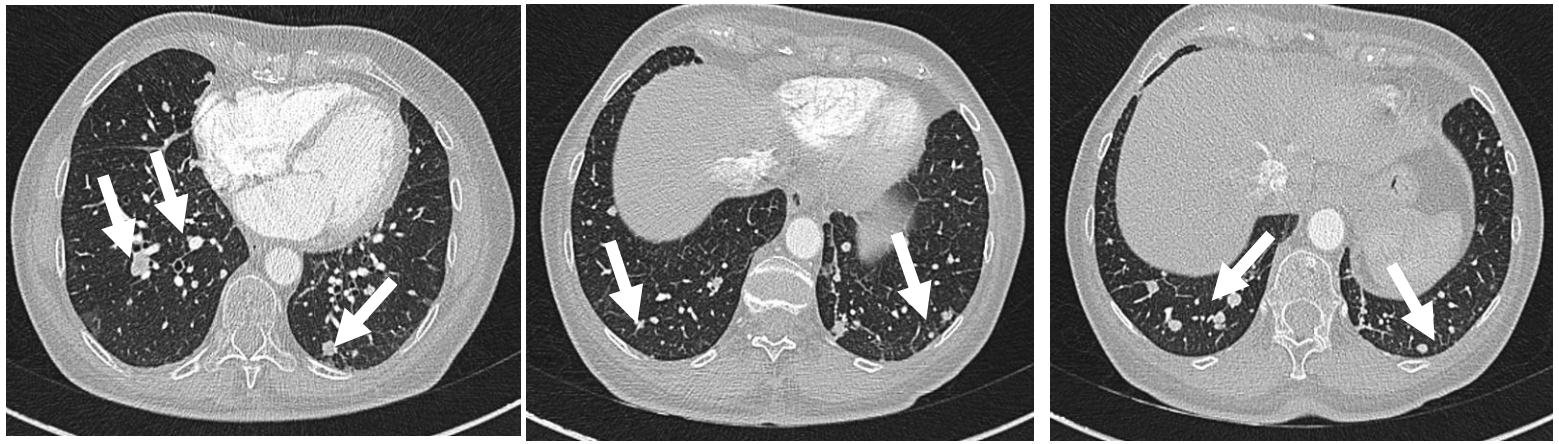
Diagnostic Work-Up

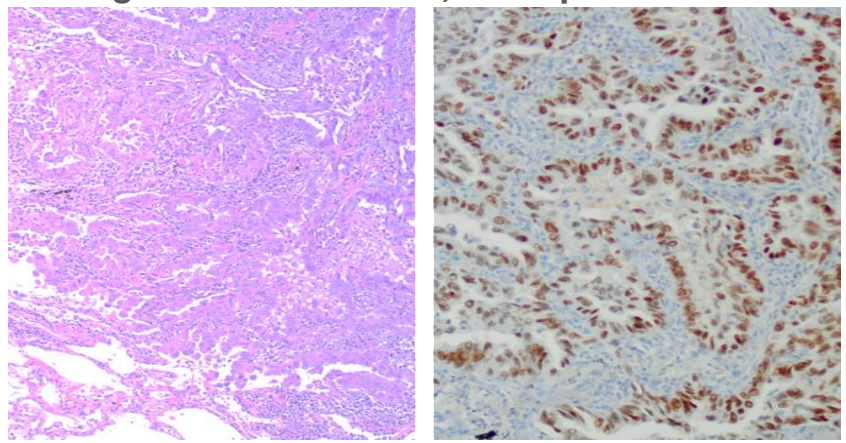
- First consultation (another center): cough, no other symptoms, ECOG PS 1, unremarkable physical exam
- CT scan: multiple bilateral nodules
- PET-CT scan: no extrathoracic metastases
- MRI: no brain metastases

- Pathology (obtained from **lung biopsy**): adenocarcinoma TTF1 and CK7 positive
- Molecular diagnosis: PD-L1 0% (**DAKO 22C3**) and **single tests** for *EGFR/ALK/ROS1* all negative

Stage IVA (Lung Metastases)



Lung adenocarcinoma, TTF1 positive



RET NTRK
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Management

- First-line therapy
  - Platinum-pemetrexed-pembrolizumab x 4 cycles followed by pemetrexed-pembrolizumab maintenance
- Best response: SD
- After 5 months, treatment had to be stopped due to progressive disease
- The patient is referred to our centre to consider participation in a clinical trial
- **New lung biopsy** is required for a complete genetic reassessment with NGS

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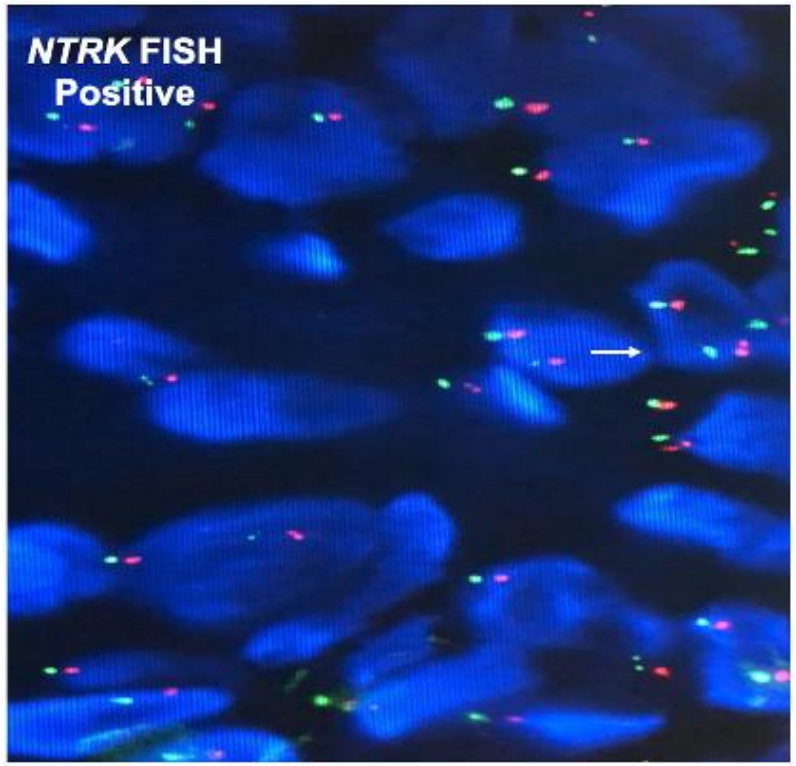
Genetic Reassessment

1. **Tissue NGS (RNA)**: positive for *NTRK1* fusion
2. **FISH**: positive for *NTRK1* fusion (30%)

FISH *NTRK* probe
ZytoLight SPEC *NTRK1* BA Probe

Dual color
5’ *NTRK*
3’ *NTRK*



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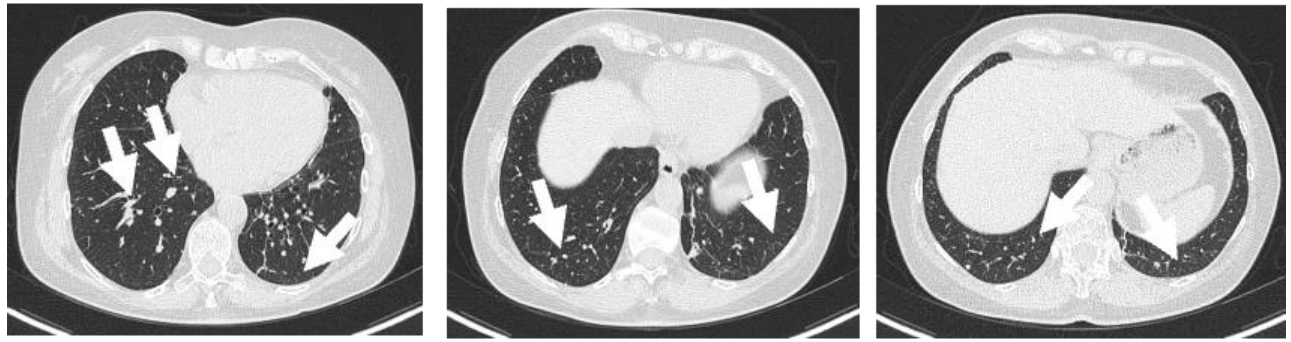
Outcome

- Treatment with **larotrectinib** 100 mg orally twice daily started
- Best objective response PR that has remained to this day (**PFS 48 mo**)
- Side effects:
  - Confusion G2
  - Dizziness G2
  - Loss of memory G1

July 2018

July 2022



RET NTRK
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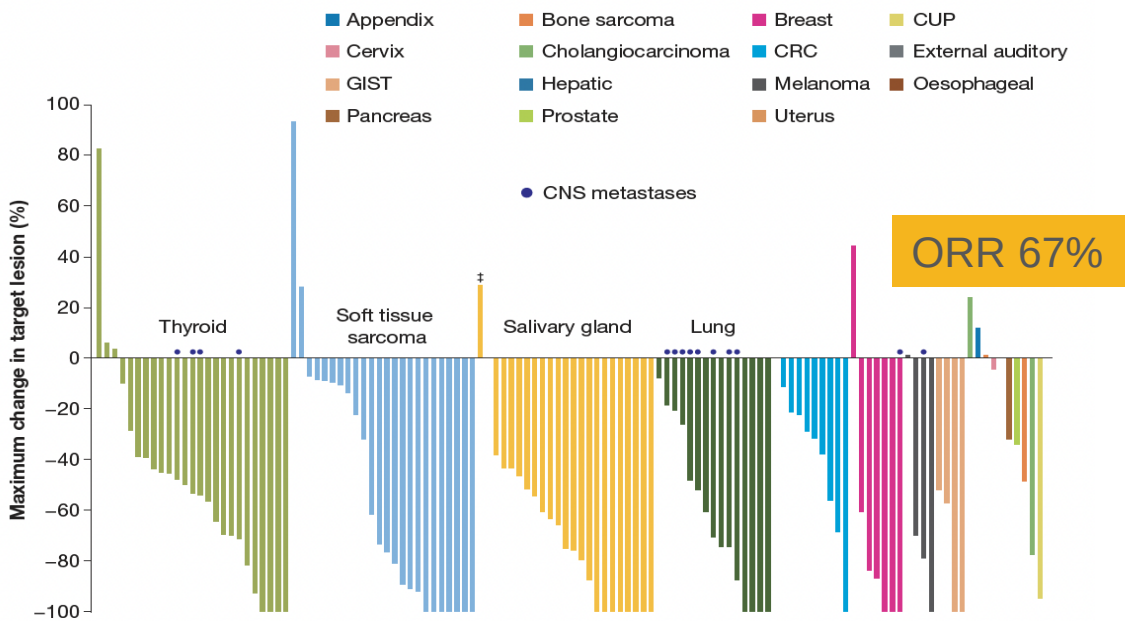
Efficacy of NTRK Inhibitors in Patients with *NTRK* Fusion Regardless of Tumor Type

Larotrectinib[1]

Expanded Integrated Dataset (n=130)[1]
(Adult Phase 1 trial, NAVIGATE)

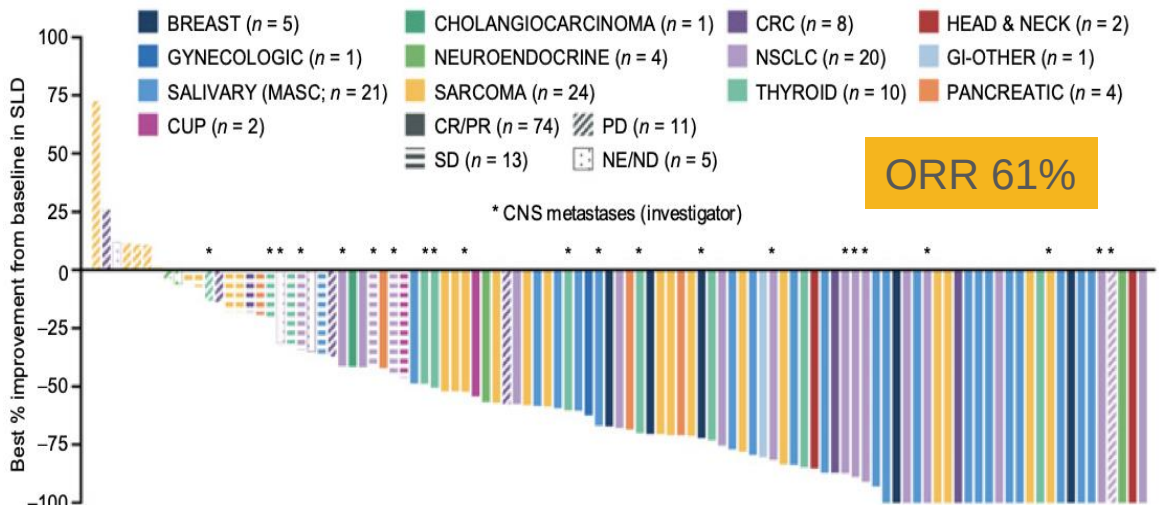


ORR 67%

Median follow-up 22-24 mo

Entrectinib[2]

Expanded Integrated Dataset (n=121)[2]
(ALKA-372-001, STARTRK-1 and STARTRK-2)



ORR 61%

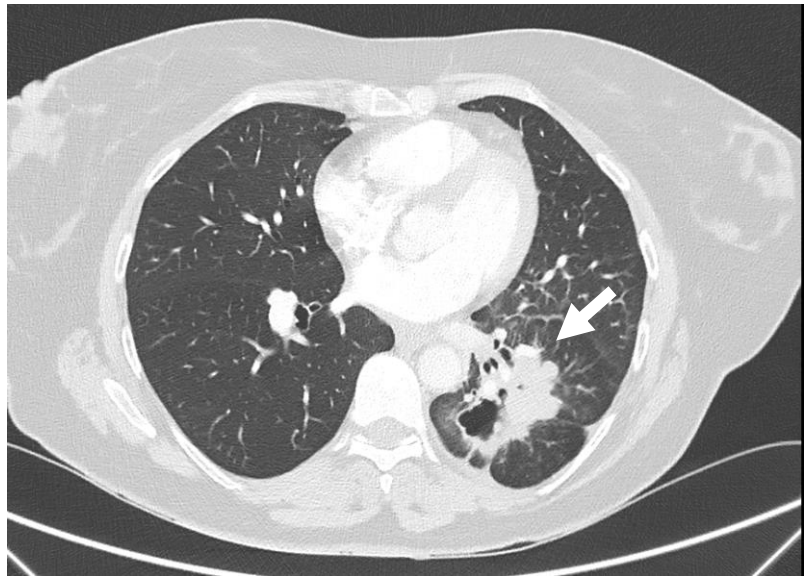
Median follow-up 25.8 mo

1. Brose MS, et al. *Ann Oncol* 2021;32(suppl 5):Abstract 535P; 2. Demetri GD, et al. *Clin Cancer Res* 2022;28:1302–12.

Clinical Case #2

Patient History

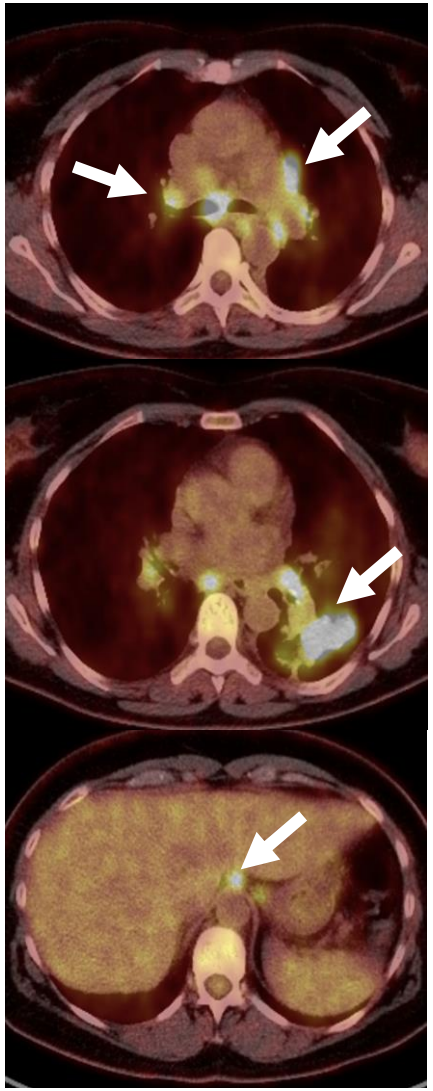
- Female, 61-year-old, teacher
- **Never smoker**
- No family history of cancer
- Medical history: Thalassemia minor
- Drug history: none
- In January 2020, recurrent episodes of deep vein thrombosis and severe asthenia
- CT scan is requested showing a lower left cavitated mass with enlarged bilateral lymph nodes



Multidisciplinary Diagnostic Work-Up

- Consultation: ECOG PS 2 and severe asthenia
- PET-CT scan: FDG uptake of the primary tumor mass, bilateral mediastinal nodes, pleura and retroperitoneum
- MRI: no brain metastases
- **Tissue biopsy**: adenocarcinoma TTF1+, PD-L1 15%, **very low cellularity content (~10%)**

LUNG ADENOCARCINOMA
cT3N3M1b, Stage IVA
(retroperitoneal lymph node)



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Molecular Testing

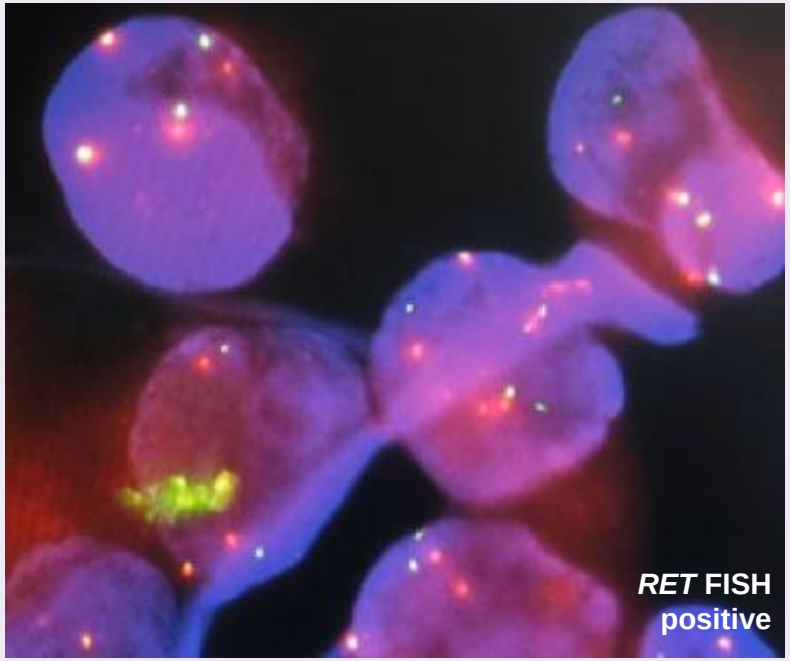
1. **Tissue NGS (RNA)**: negative
2. **Liquid biopsy (cfDNA)**: *RET-KIF5B* (0.5%)

➔ Orthogonal confirmation: **FISH** positive for *RET* fusion (90%)

Liquid biopsy (cfDNA) tumor map

Alteration	% cfDNA or Amp
RET-KIF5B Fusion	0.5%
KIF5B-RET Fusion	0.3%
ESR1 T574N	0.3%

FISH *RET* probe
ZytoLight SPEC *RET* BA



Dual color
5' *RET*
3' *RET*

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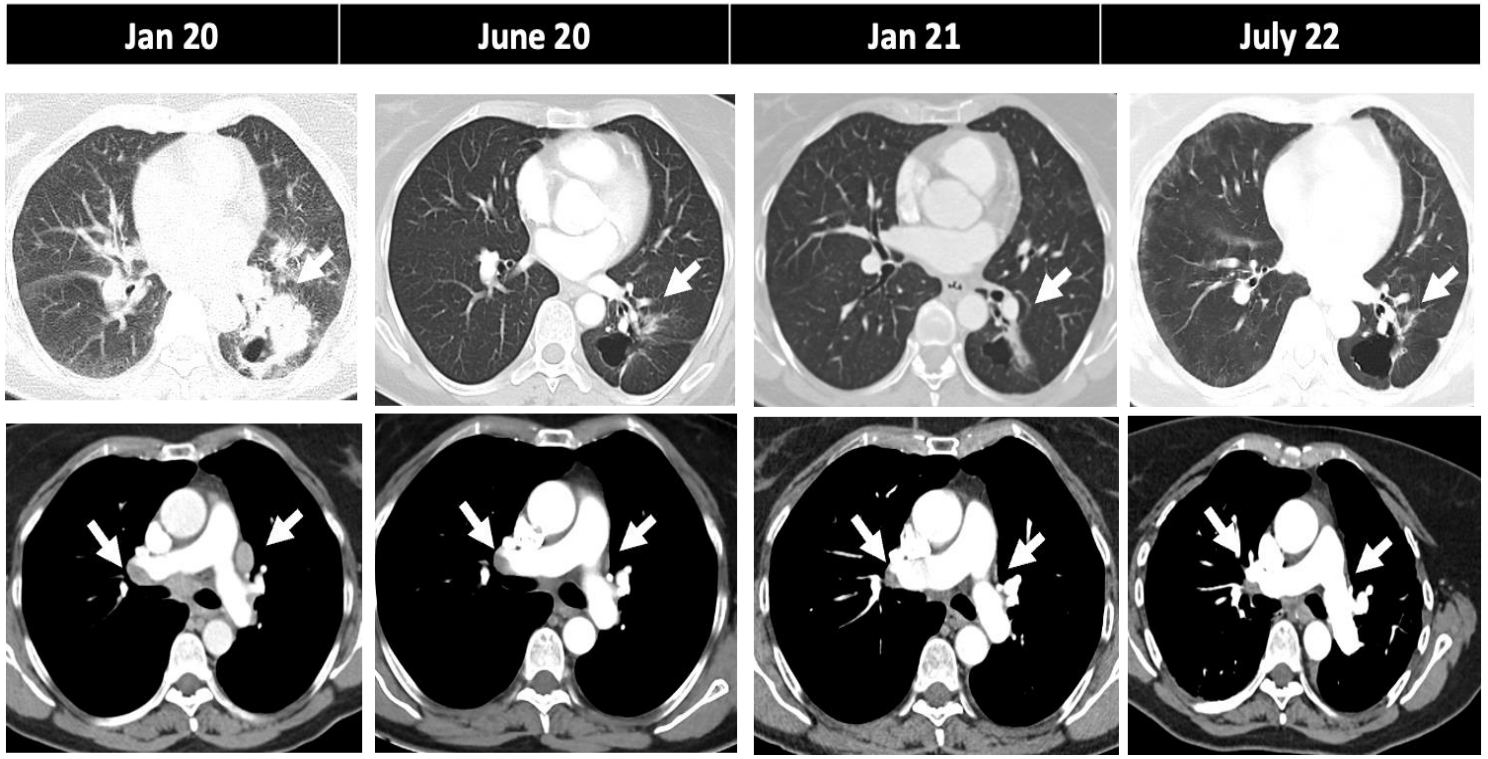
Outcome



- Treatment with selpercatinib 160 mg orally twice daily
- Rapid improvement of symptoms and ECOG PS (2 to 1)
- Best objective response PR that has remained to this day (**PFS 31 mo**)
- Side effects:
  - Diarrhea G1
  - ALT/AST increase G1
  - Fatigue G1

Thank You!

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