Update in thoracic pathology

advances in the use of molecular analysis in lung cancer

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Disclosures

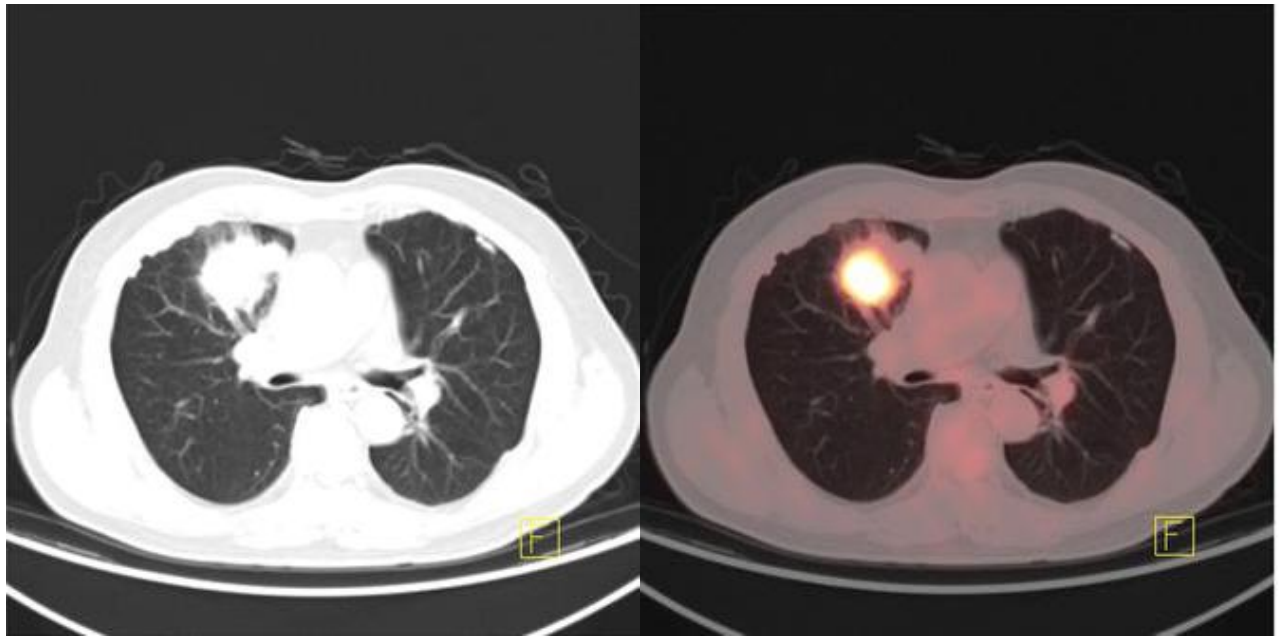
- None (no honoraria or company-sponsored research)

Overview

- Treatment and predictive testing
- Diagnostic molecular analysis
- Difficulties in large cell neuroendocrine carcinoma (LCNEC)

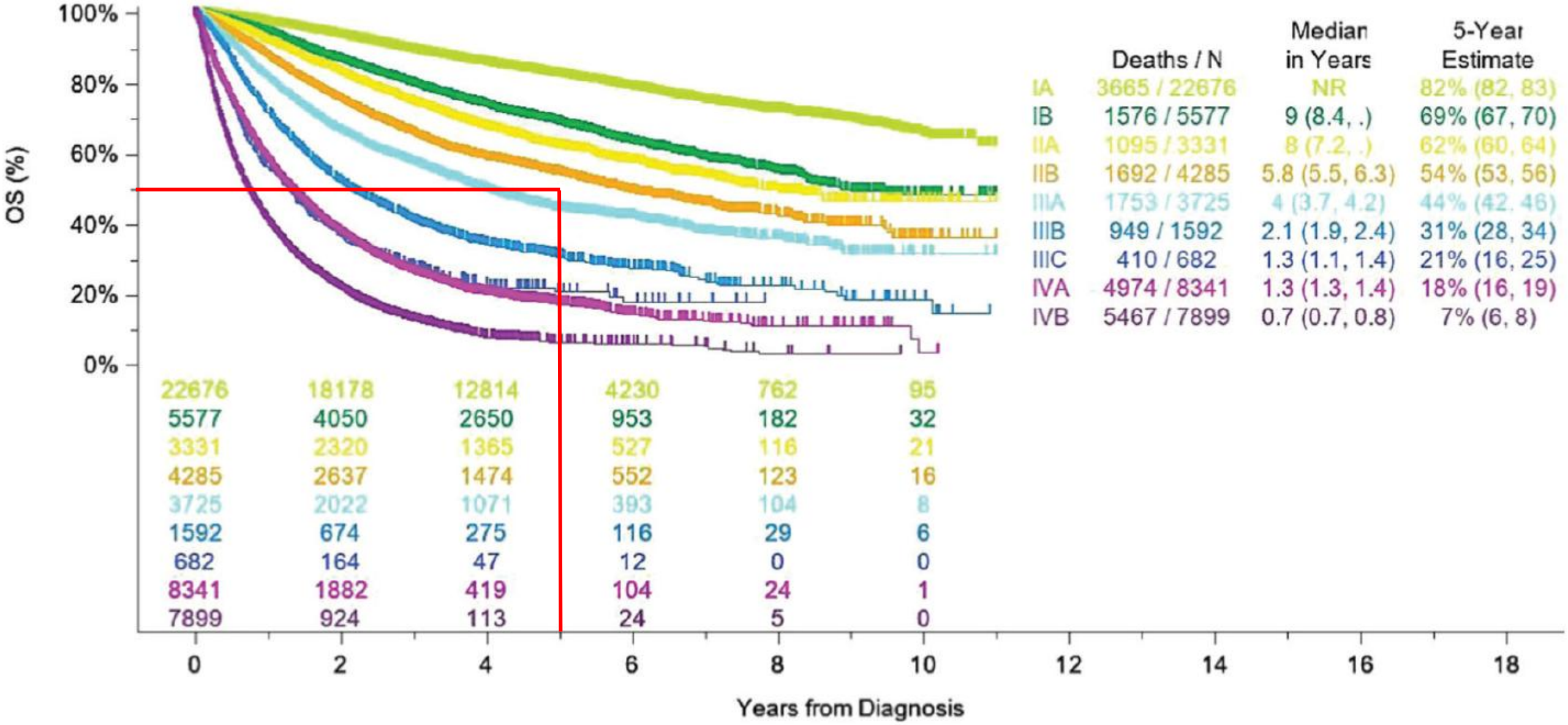
Lung cancer – basis for treatment

- Histological type
- Stage
- Treatment predictive alterations
- Patient's general condition and will



From Medical Imaging, Yongxia Zhou (ed)

Overall survival in lung cancer by stage



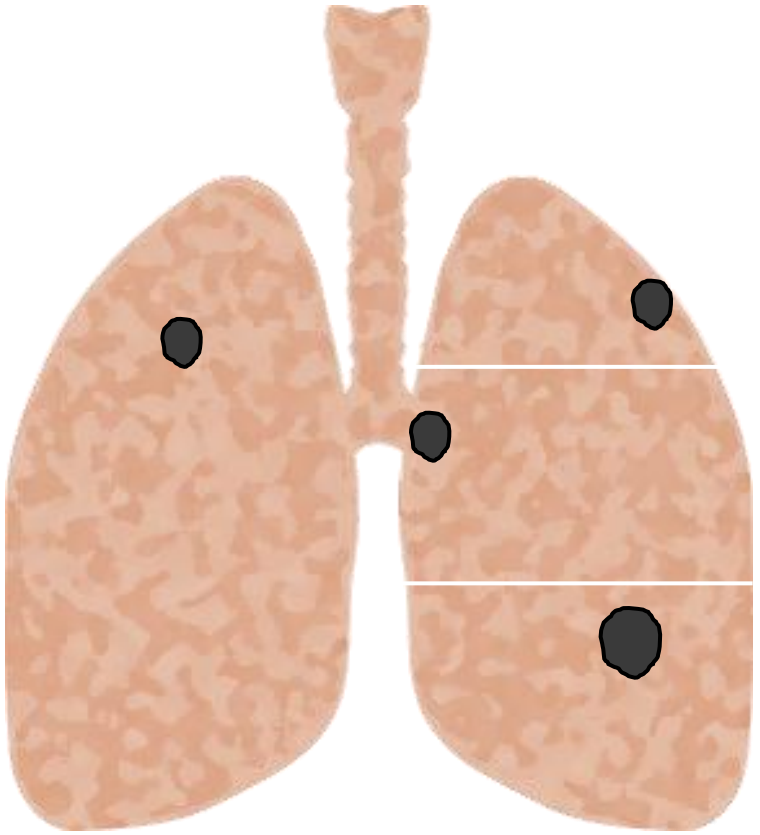
From the IASLC TNM9 staging manual 3rd edition 2024

Stage IA

Size ≤3 cm
(invasive area)

No invasion of pleura
or main bronchus

Surgery or
stereotactic RT



Stage IB

Size 3-4 cm
or pleural (incl.
adjacent lobe)
or central invasion

EGFR/ALK+ surgery +
EGFR/ALK TKI

EGFR/ALK- surgery ±
adjuvant chemo

Stage II-IIIA (some)

Size >4 cm

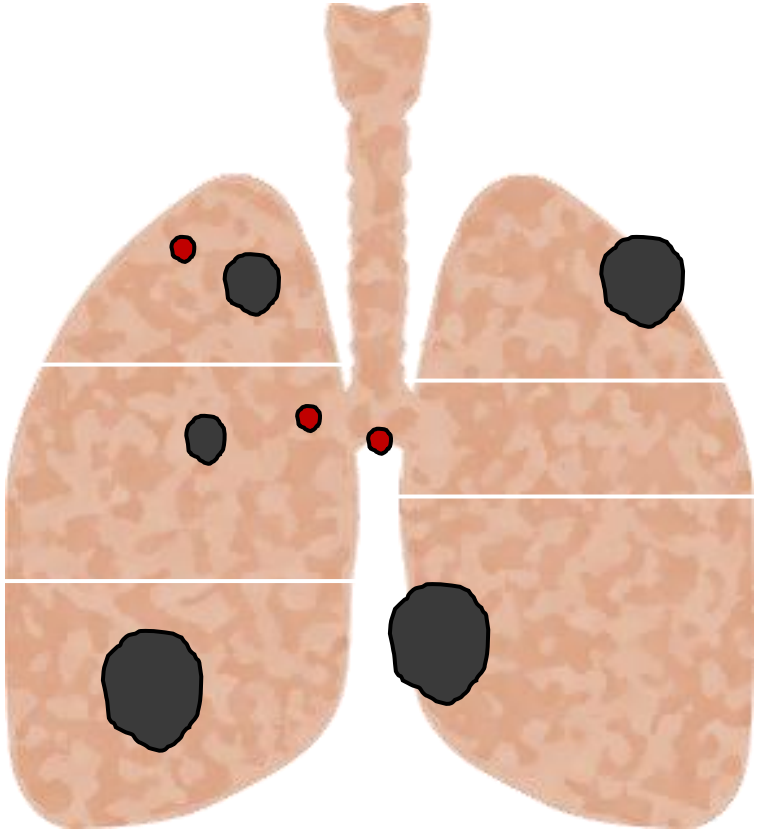
or N1 or N2 (if small tumor)

or intrapulmonary metastsis

or invasion of e.g. chest wall, mediastinum, or phrenic nerve

EGFR/ALK+ surgery + EGFR/ALK TKI

EGFR/ALK- PD-L1- surgery + adjuvant chemotherapy



EGFR/ALK- PD-L1+ surgery + neoadjuvant chemo-immunotherapy

Stage III

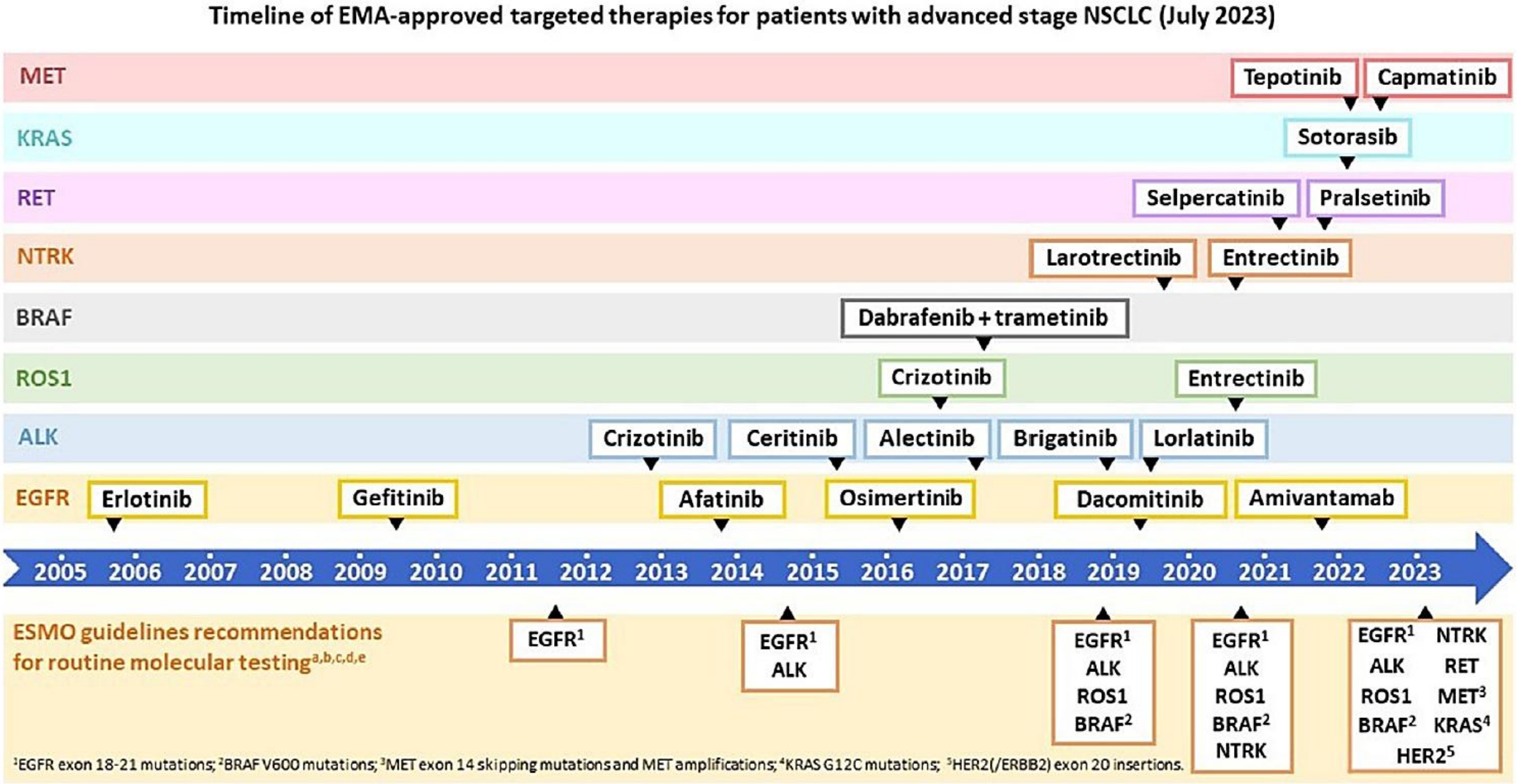
Locally advanced (incl. contralateral node mets) but no distant mets

- EGFR+ chemo-RT + EGFR TKI
- EGFR- PD-L1+ chemo-RT + immunotherapy
- EGFR- PD-L1- chemo-RT

Stage IV

Metastasis to pleura, contralateral lung, or extrathoracic site

- EGFR/KRAS G12C/ERBB2/ BRAF V600/MET ex14/ ALK/ROS1/RET/NTRK+ TKI (1st or 2nd line)
- Otherwise chemo-immunotherapy



PMID: 38476742

- Handled as adenocarcinoma
  - Adenocarcinoma
  - Non-small cell carcinoma (NSCC) probably adenocarcinoma
  - NSCC not otherwise specified (NOS)
  - Large cell carcinoma
  - Adenosquamous carcinoma
  - Sarcomatoid carcinoma
  - Thoracic SMARCA4 deficient undifferentiated tumor
- Handled as squamous cell carcinoma
  - Squamous cell carcinoma
  - NSCC probably squamous cell ca
  - Lymphoepithelial carcinoma
- Handled as small cell carcinoma
  - Small cell carcinoma
  - Large cell neuroendocrine carcinoma (LCNEC)
  - Neuroendocrine carcinoma NOS
- Other lung carcinomas
  - Salivary gland type carcinoma
  - Carcinoid tumor
  - NUT carcinoma
- Non-epithelial tumors
  - Sarcomas, lymphomas, melanoma
- Metastases to the lung

Treatment-predictive testing of lung carcinomas

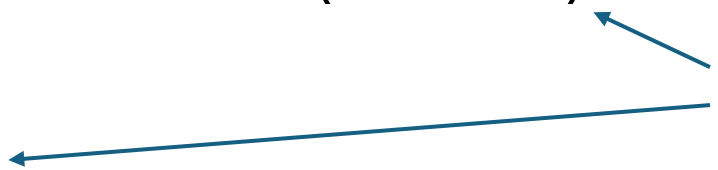
TESTING

- Non-small cell carcinoma (stage IB-IV)

  (different chemo for adenocarcinoma and squamous cell carcinoma)

NO TESTING

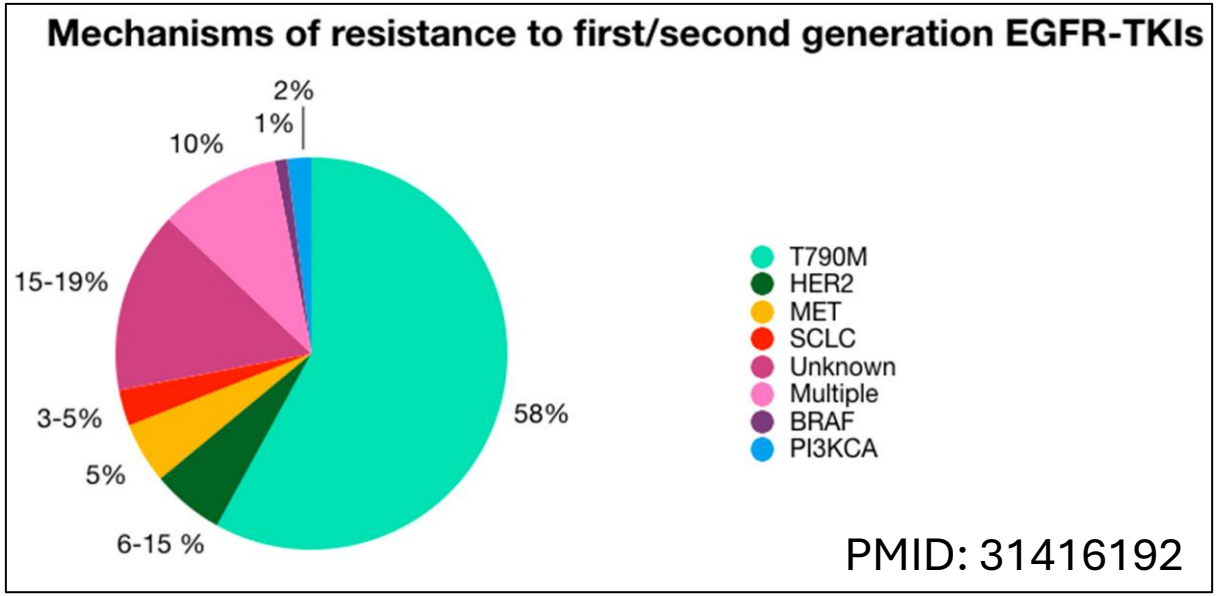
- Small cell carcinoma
- Large cell neuroendocrine carcinoma (LCNEC)
- Carcinoid tumor
- Salivary gland carcinomas

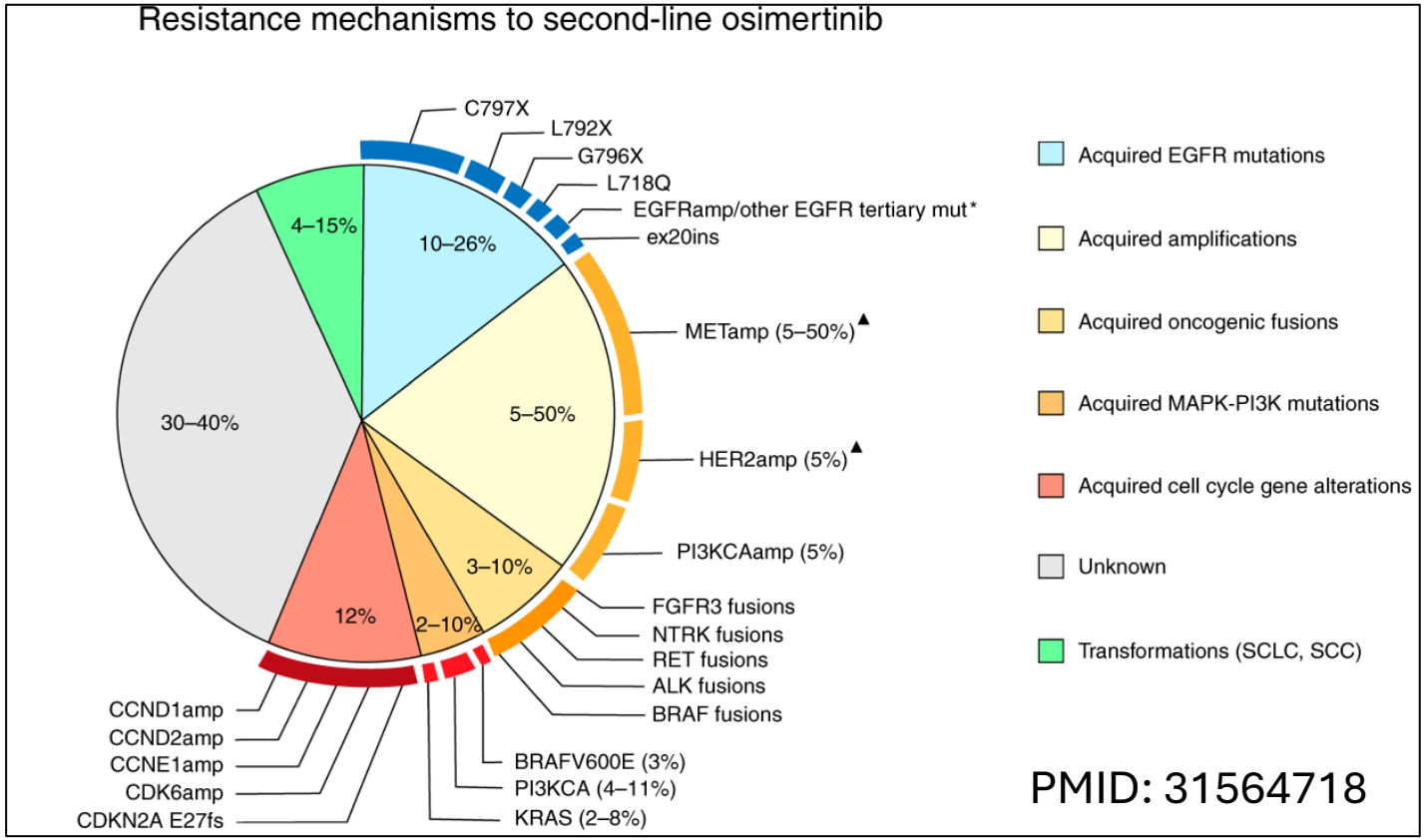


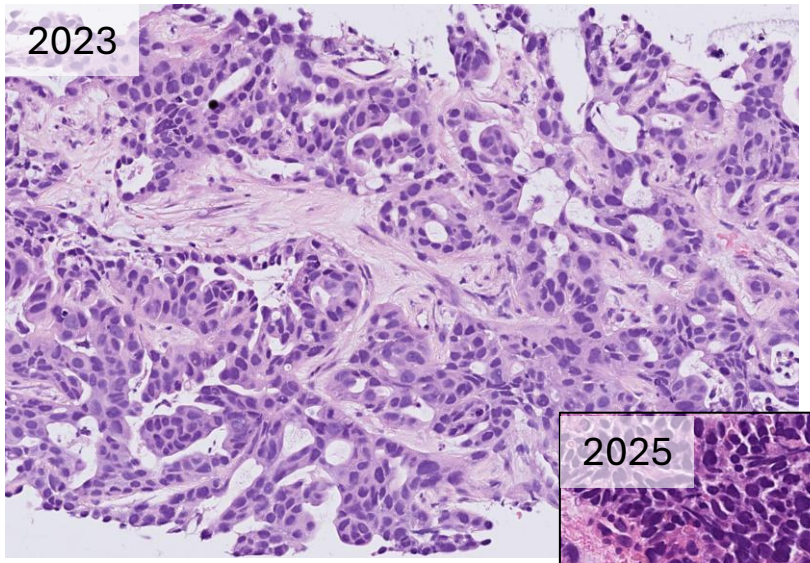
If certain diagnosis

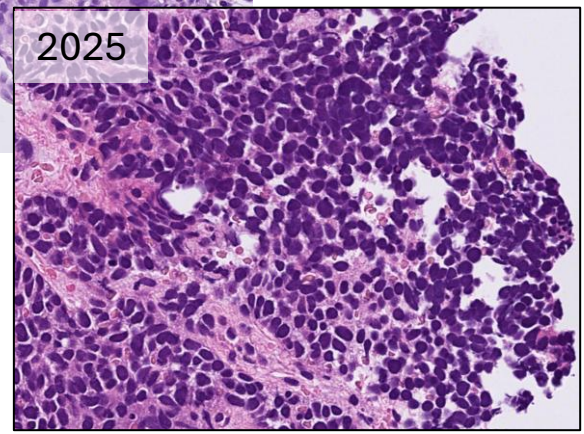
Testning in the TKI resistance situation

- EGFR T790M (→ osimertinib)
- Other EGFR mutation
- Other mutation/fusion/amplification
- Small cell transformation
- Unknown mechanism



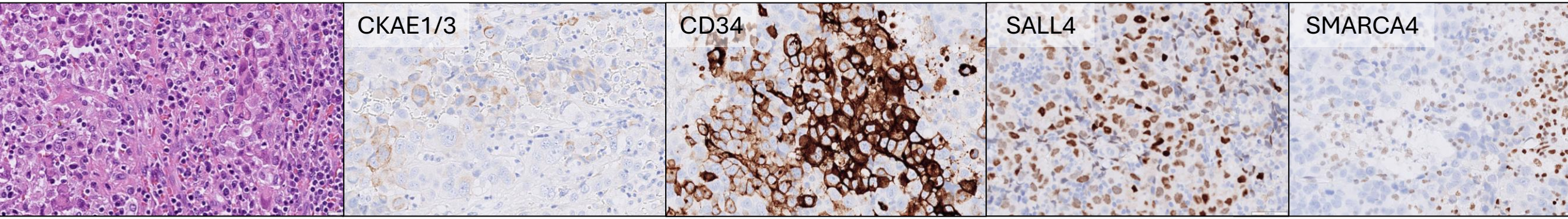




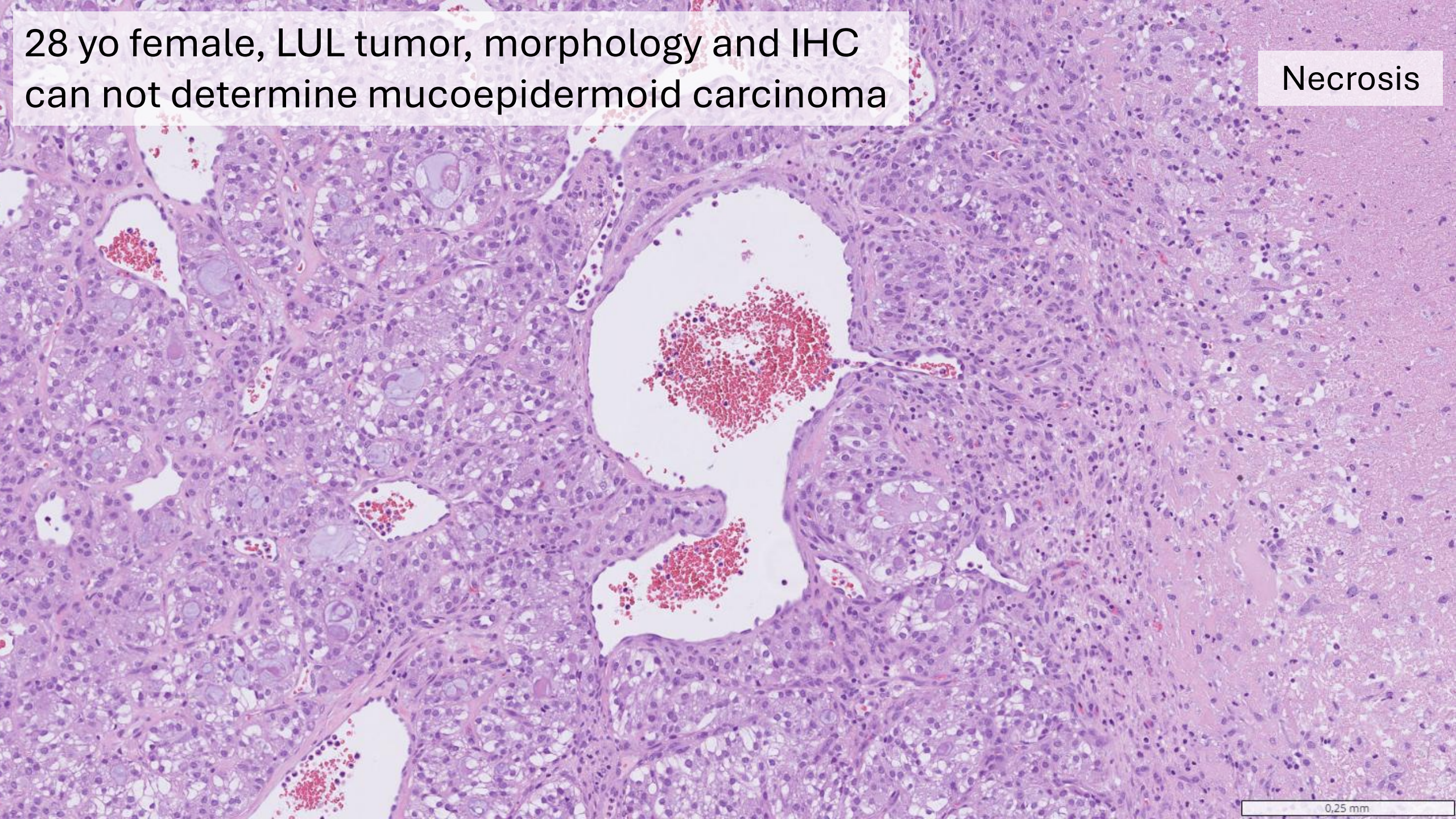


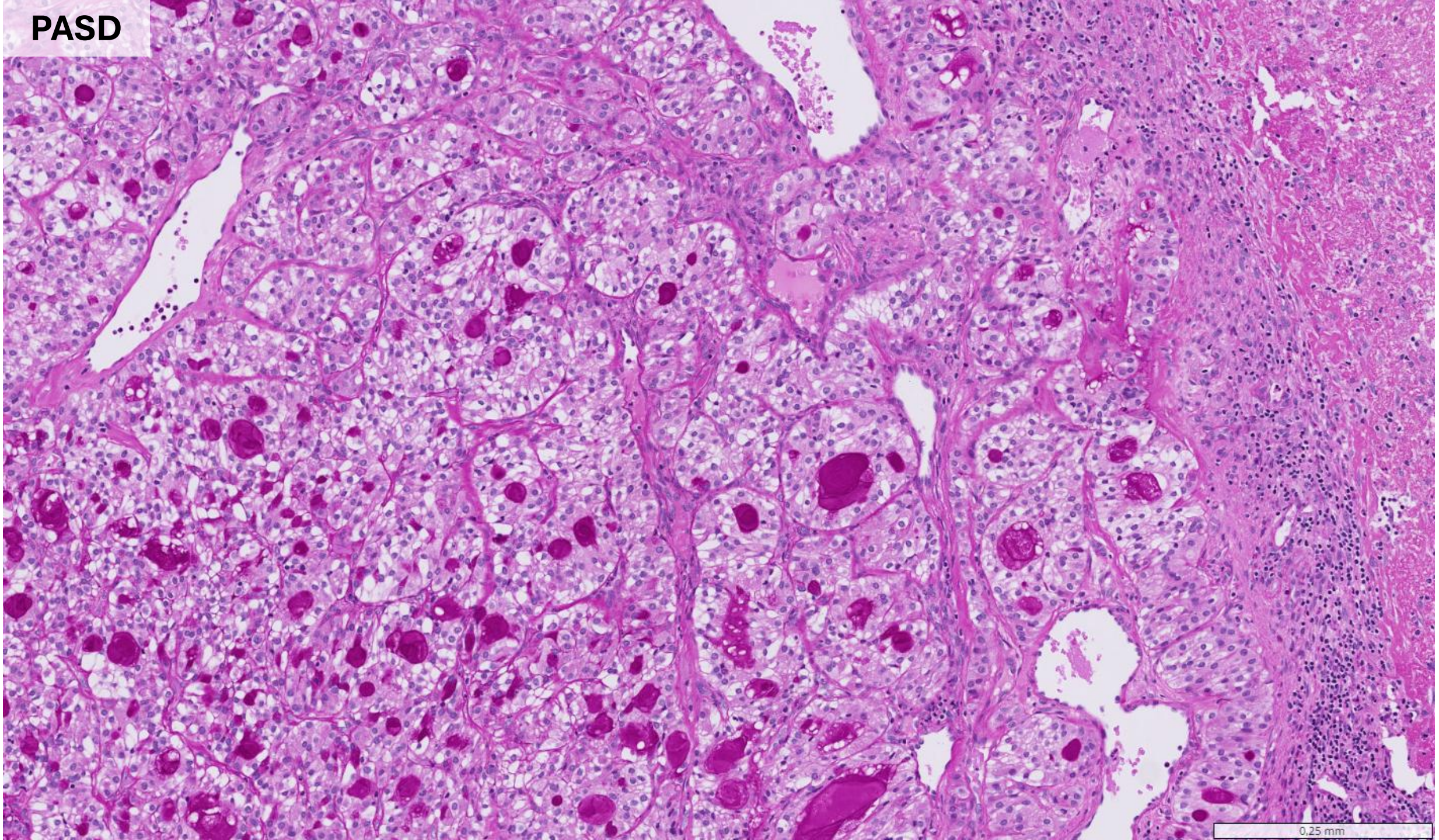
Diagnostic molecular analysis – ”type-specific” alterations

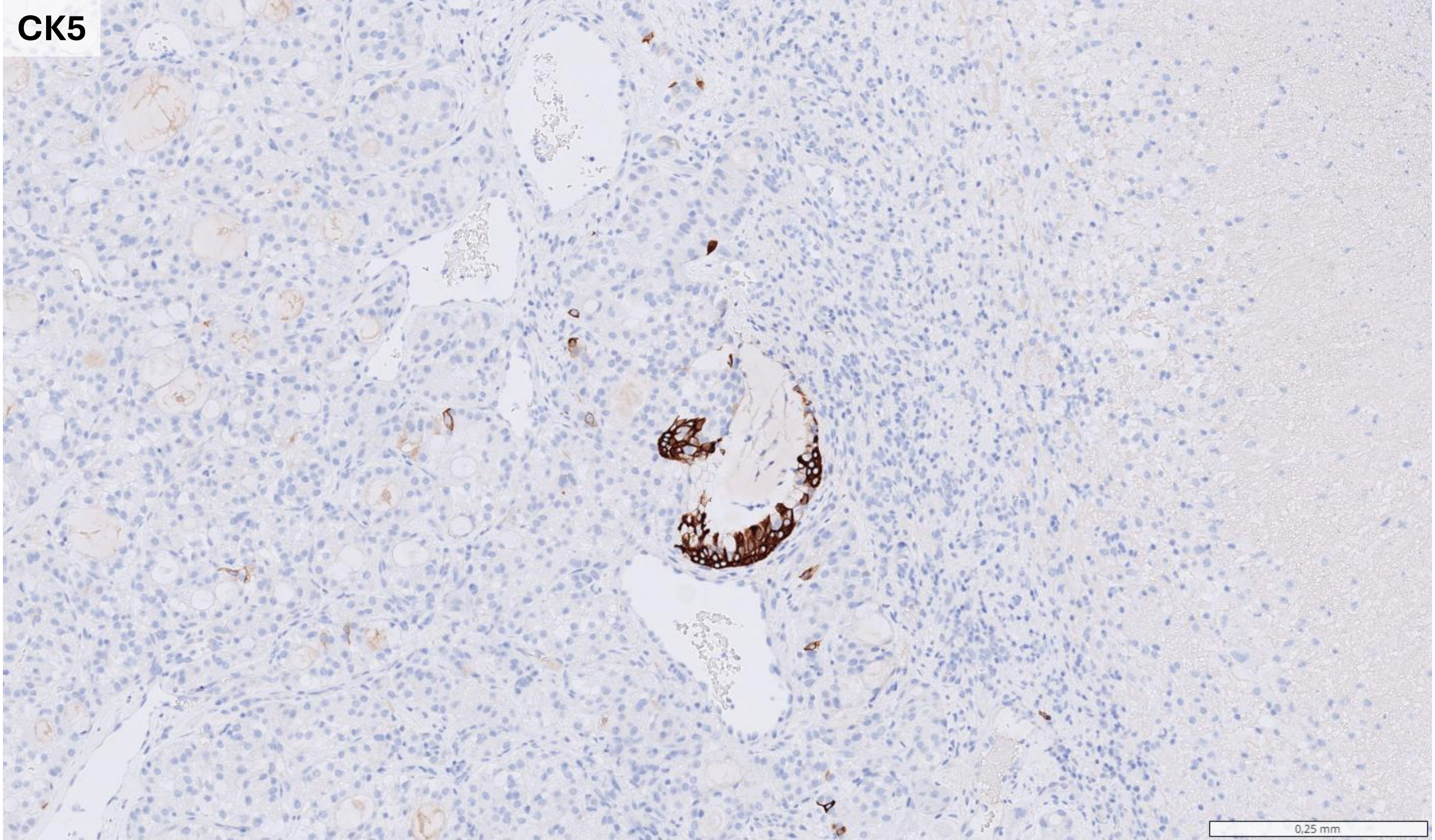
• MAML2 fusion	mucoepidermoid carcinoma
• SMARCA4 mutation	thoracic SMARCA4-deficient undifferentiated tumor
• NUT fusion	NUT carcinoma
• RB1 mutation/deletion	high-grade neuroendocrine carcinomas

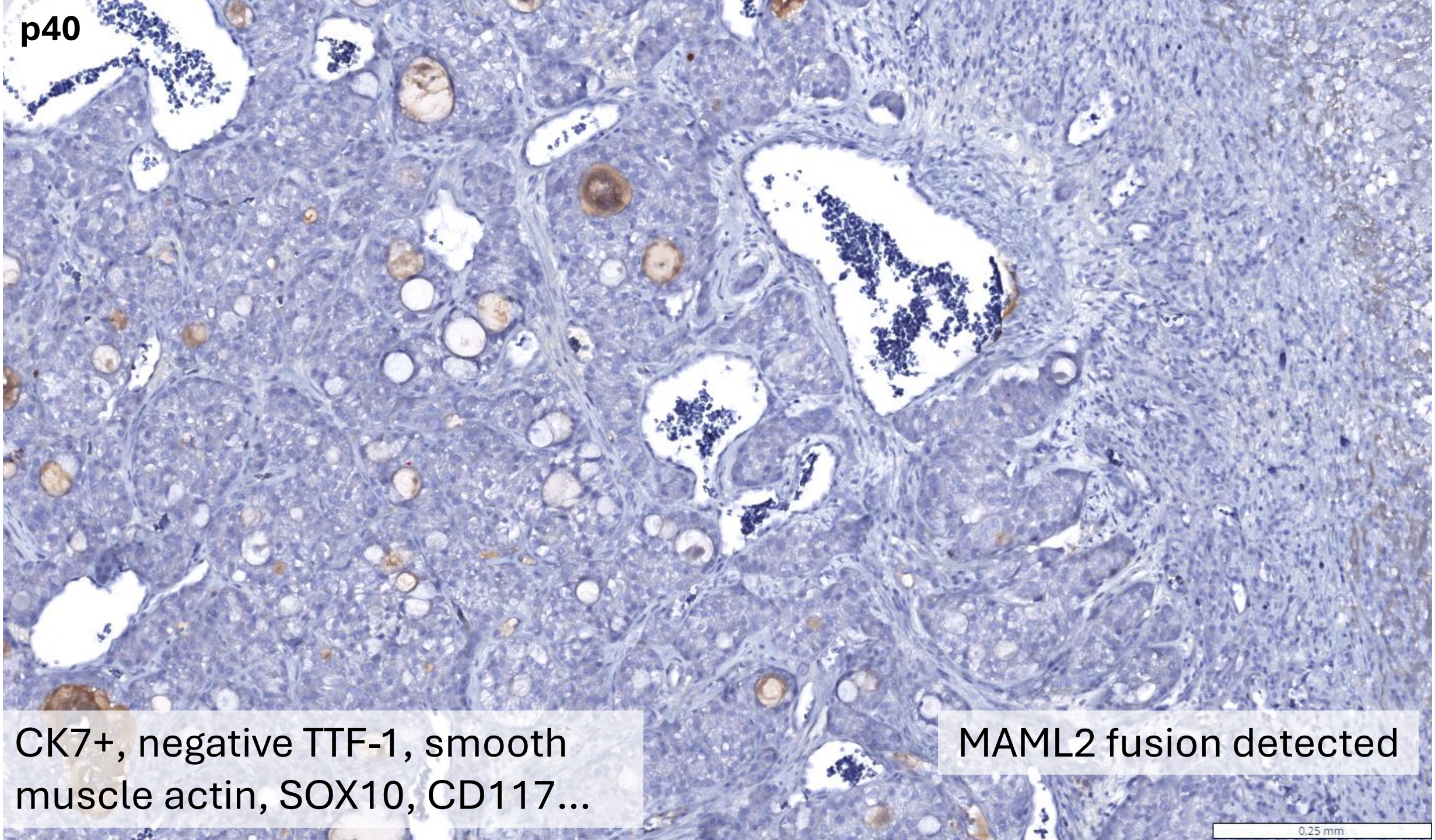


28 yo female, LUL tumor, morphology and IHC can not determine mucoepidermoid carcinoma

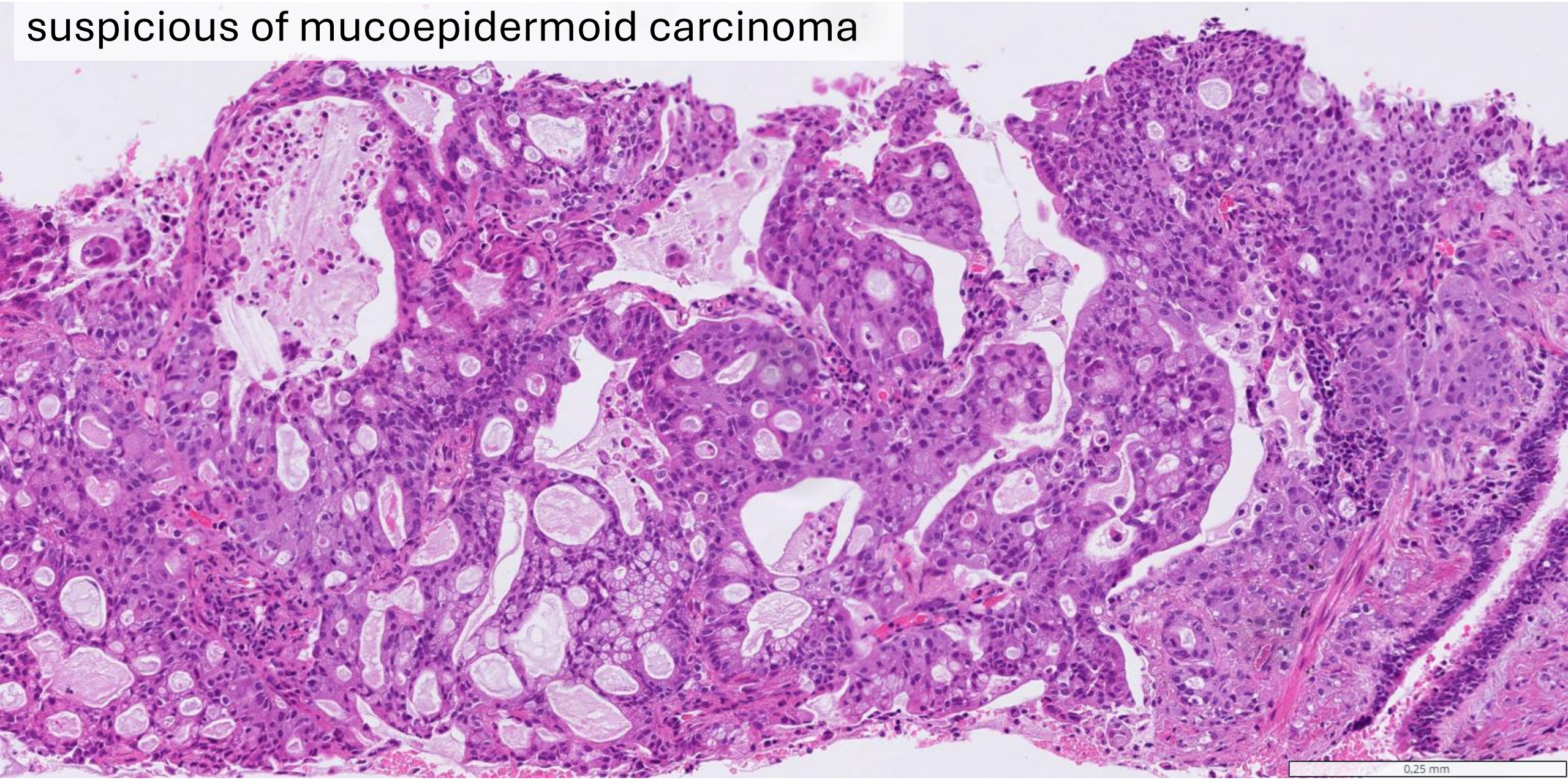


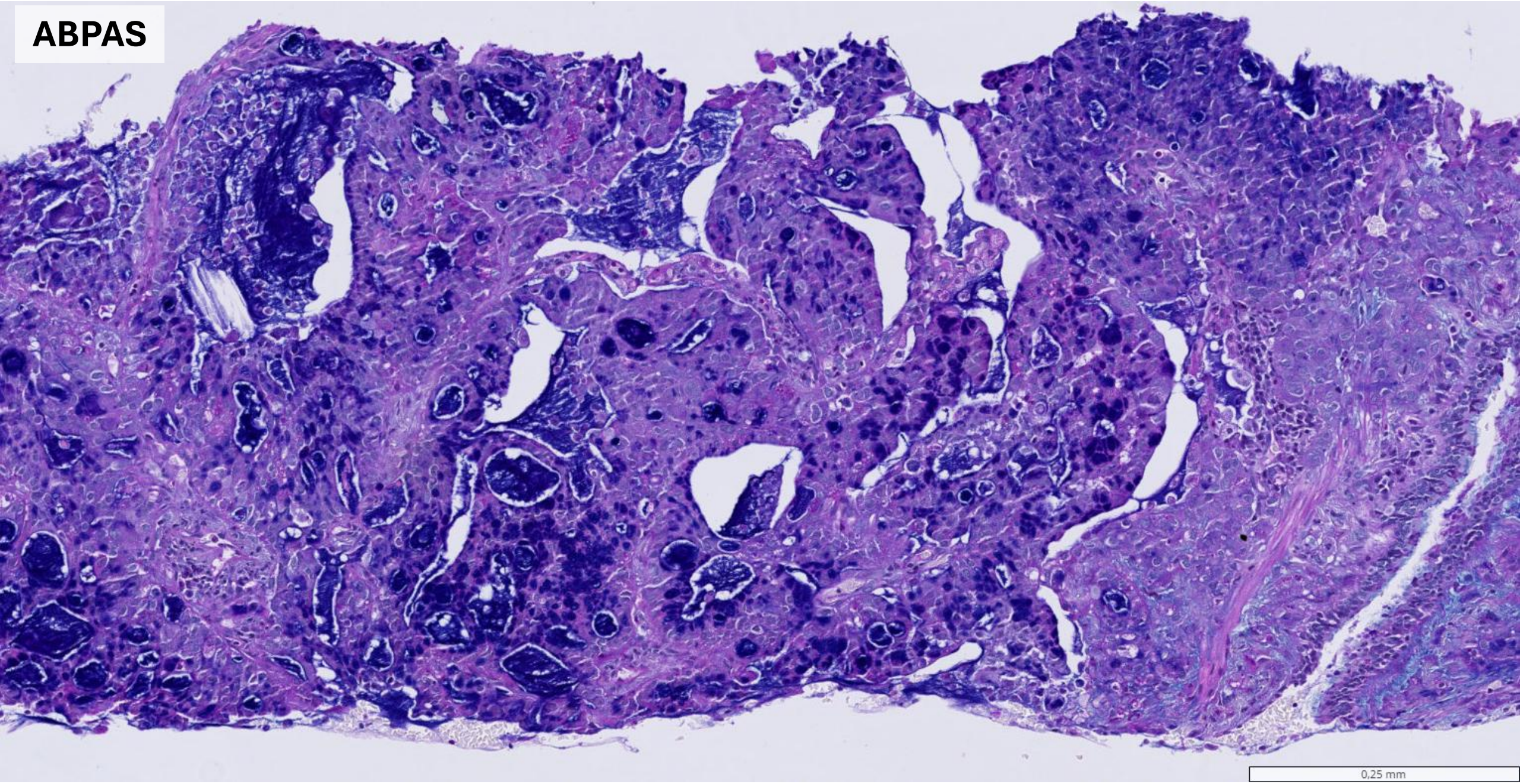

PASD
0,25 mm

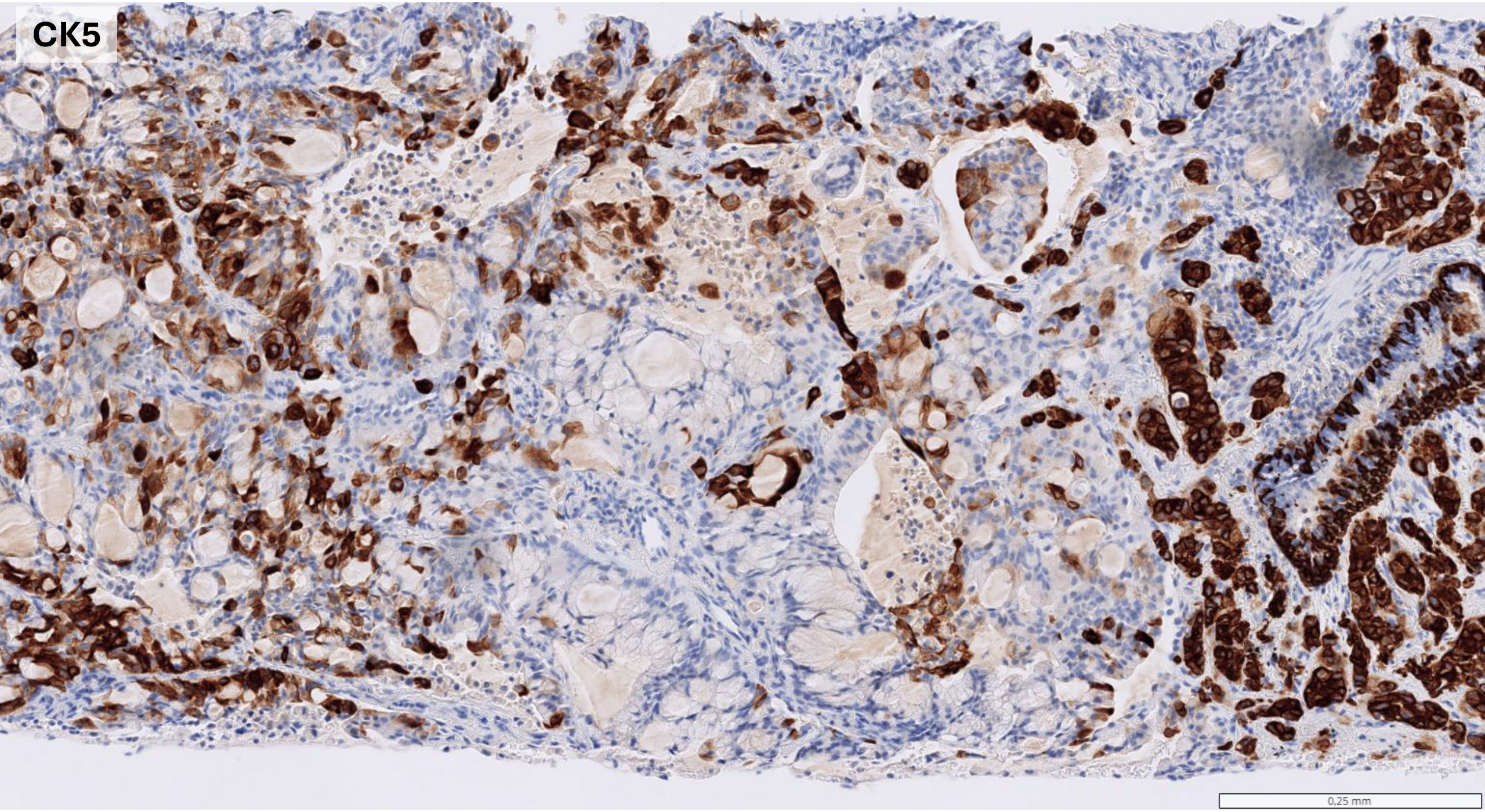

CK5
0,25 mm

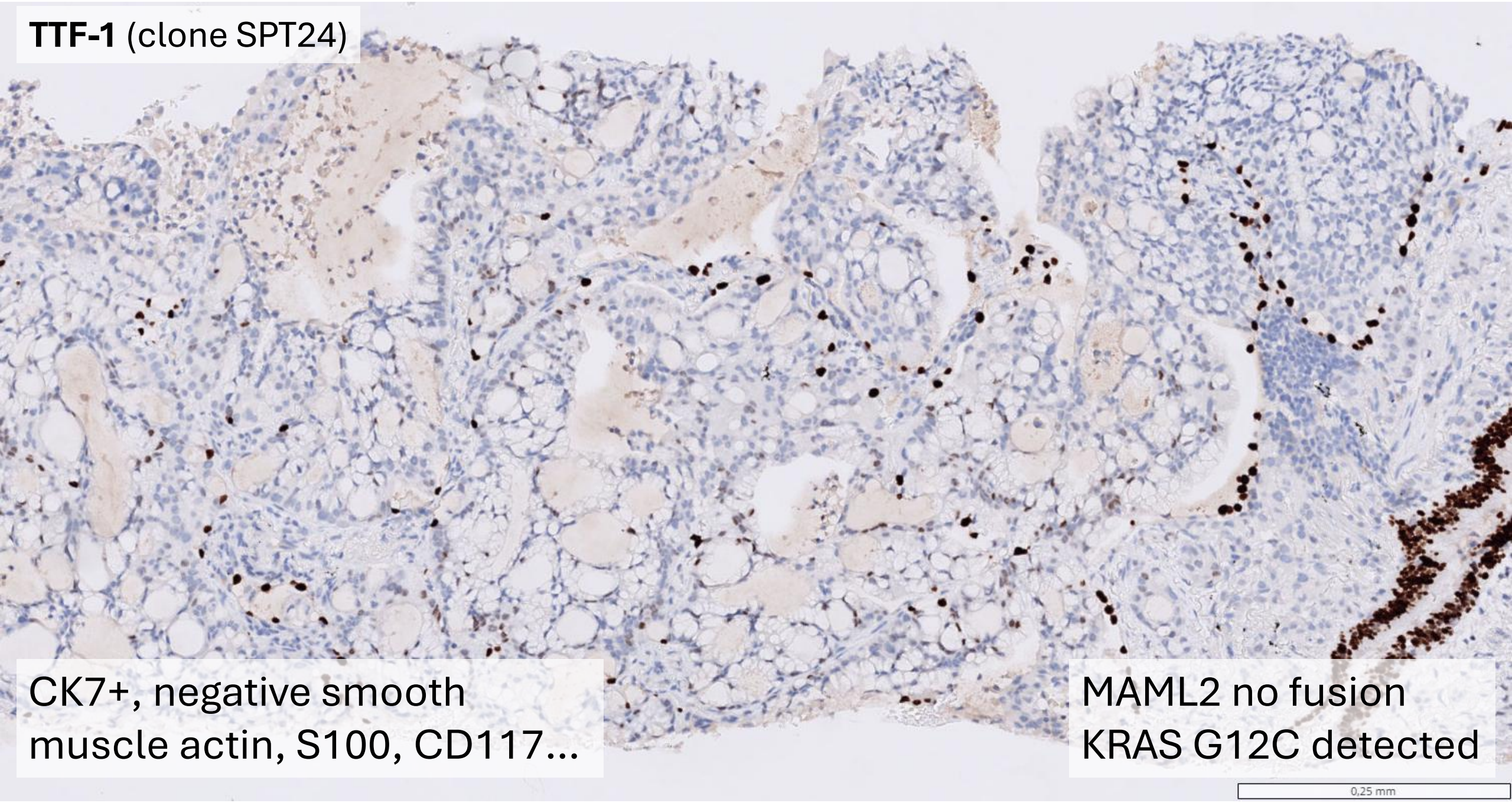

p40
CK7+, negative TTF-1, smooth muscle actin, SOX10, CD117…
MAML2 fusion detected
0,25 mm

80 yo male, LLL tumor, morphology and IHC suspicious of mucoepidermoid carcinoma

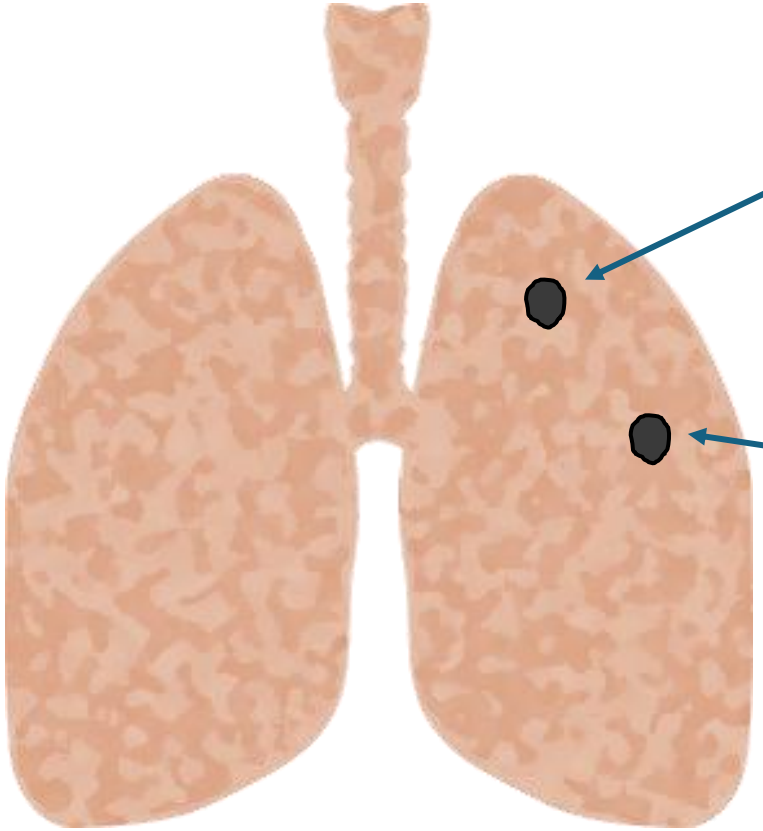



ABPAS
0,25 mm

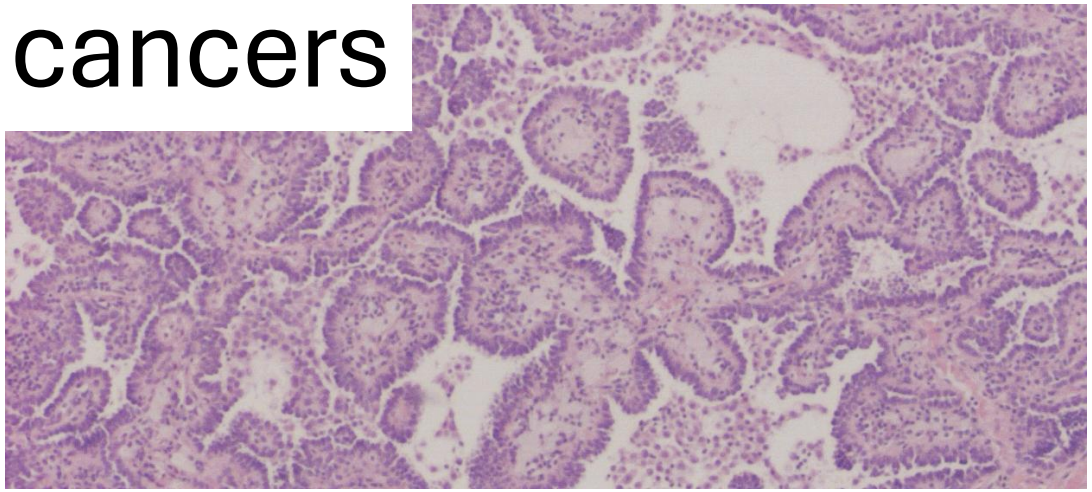

CK5
0,25 mm

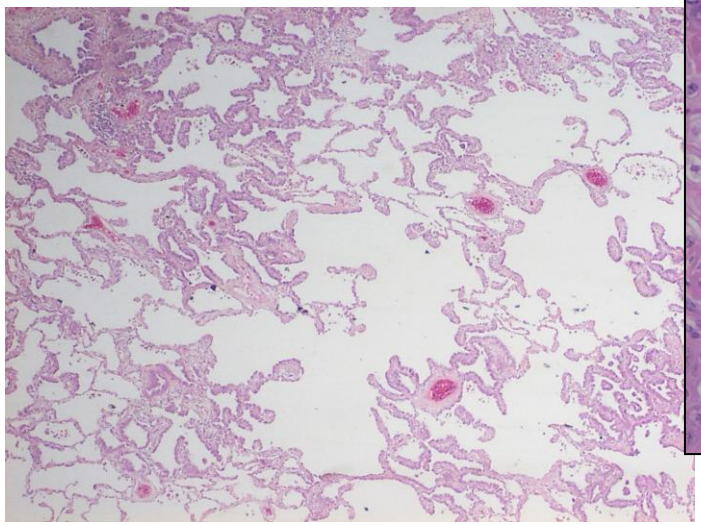

TTF-1 (clone SPT24)
CK7+, negative smooth muscle actin, S100, CD117…
MAML2 no fusion
KRAS G12C detected
0,25 mm

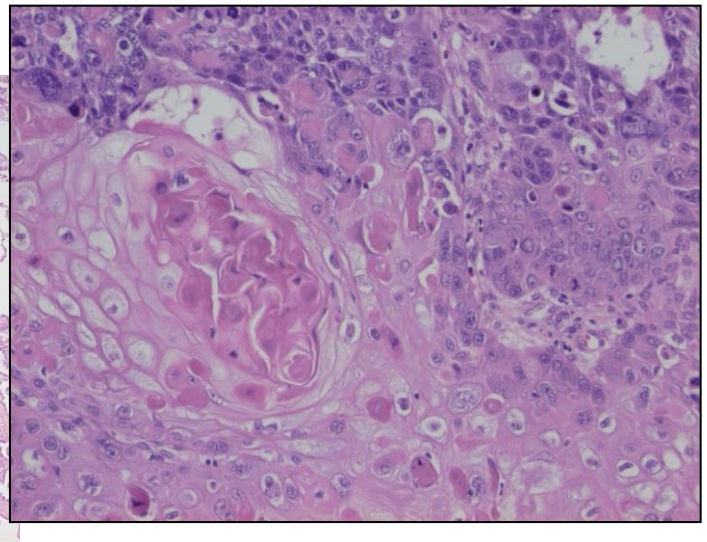
Diagnostic molecular analysis – staging/multiple lung cancers



Adenocarcinoma







Squamous cell carcinoma

Minimally invasive or adenocarcinoma in situ

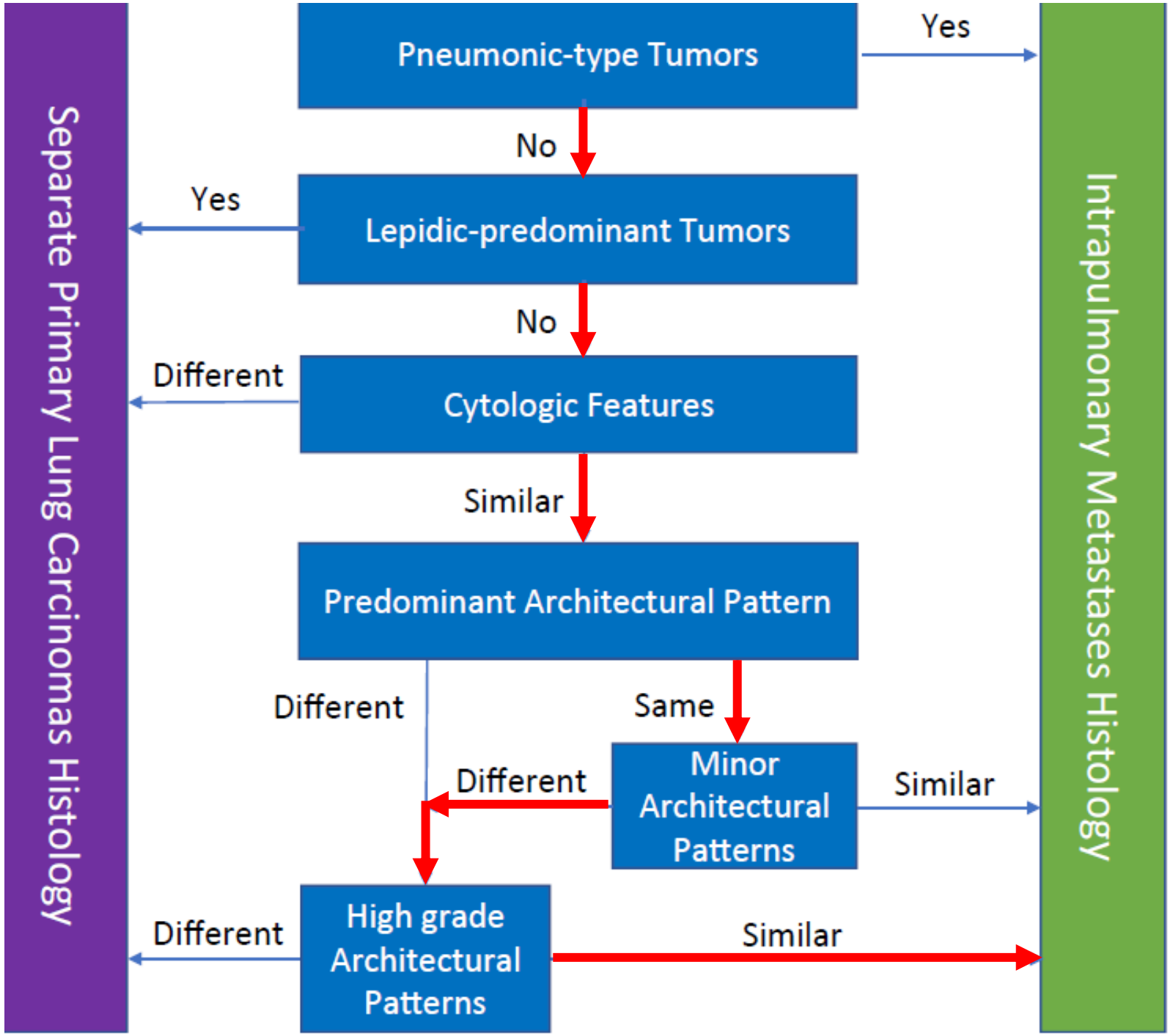
The IASLC method for multiple adenocarcinomas

PMID: 39579981

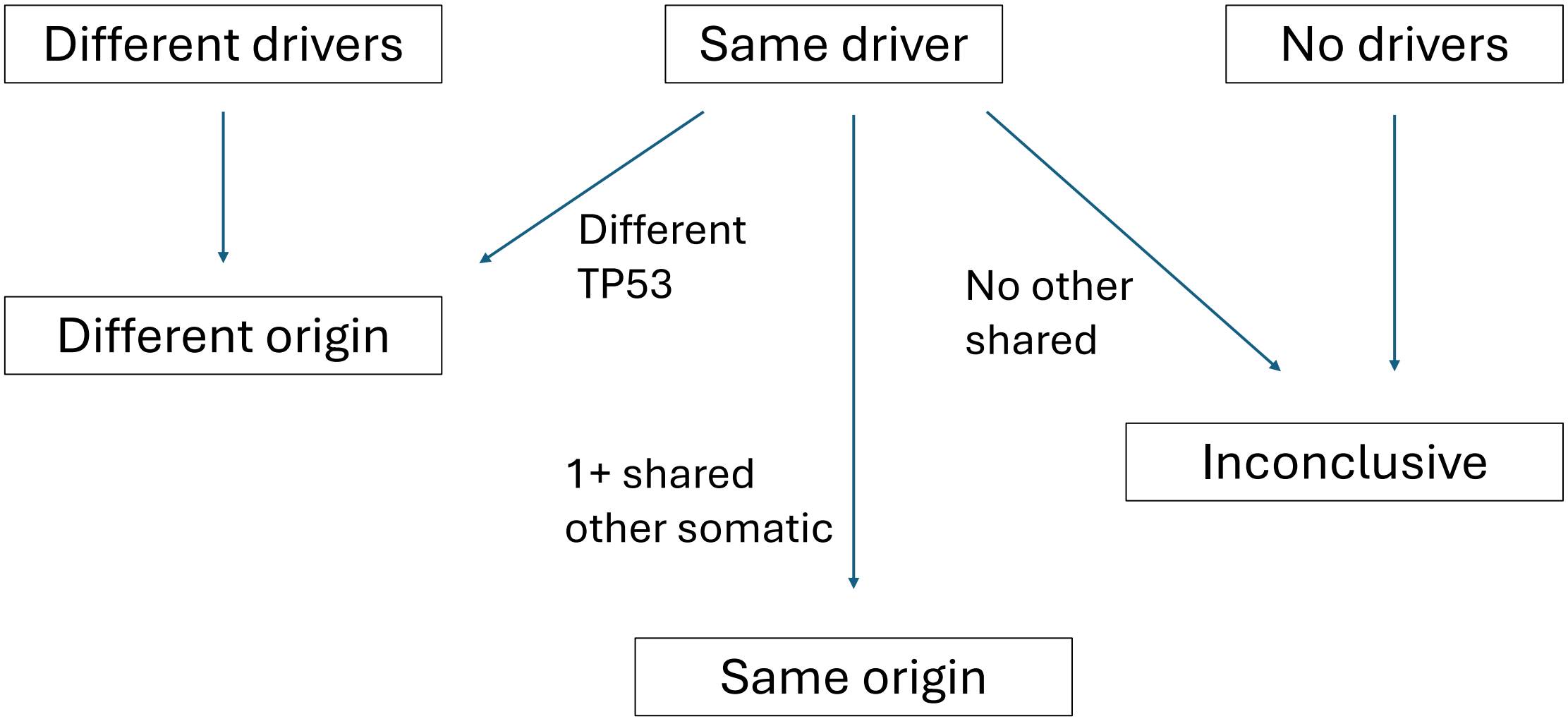
- Morphology
  - Certain types
  - Comparison of growth patterns

78-87% concordance with NGS ≈400 genes (PMID: 31471310, 36788096)

- Driver mutation analysis
- Larger NGS or e.g. loss of heterozygosity, comparative genomic hybridization, genomic breakpoints



IASLC interpretation of molecular profiling



MODERN PATHOLOGY

USCAP UNITED STATES AND CANADIAN ACADEMY OF PATHOLOGY

Journal homepage: https://modernpathology.org/

Review Article

Pathologic Assessment and Staging of Mult Carcinomas: A Paradigm Shift with the Em Methods

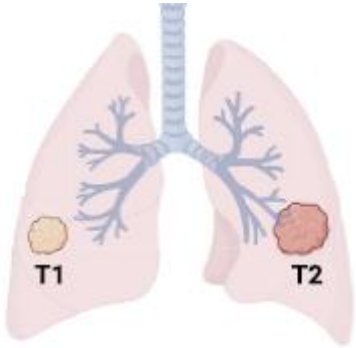
Jason C. Chang, Natasha Rekhtman*

PMID: 38387831

- Limitations of growth patterns favour molecular analysis
- Risk of false negative results (e.g. low TC)
- High-prevalence drivers are uninformative (KRAS in Westerns with smoking history, EGFR in never-smokers/Asians)

Interpreting driver-only testing

Driver A (KRAS)	Driver B (EGFR)	Definite SPLC (30%)
Driver Any	No Driver^	Likely SPLC (28%) (^borderline tumor content can cause false negative results)
Uncommon Driver D (ERBB2*)	Uncommon Driver D (ERBB2*)	Likely IPM (21%) (*ERBB2 exon20 mutation prevalence ~2%)
Common Driver C (KRAS G12C)	Common Driver C (KRAS G12C)	Uninformative (9%)
No Driver	No Driver	Uninformative (12%)

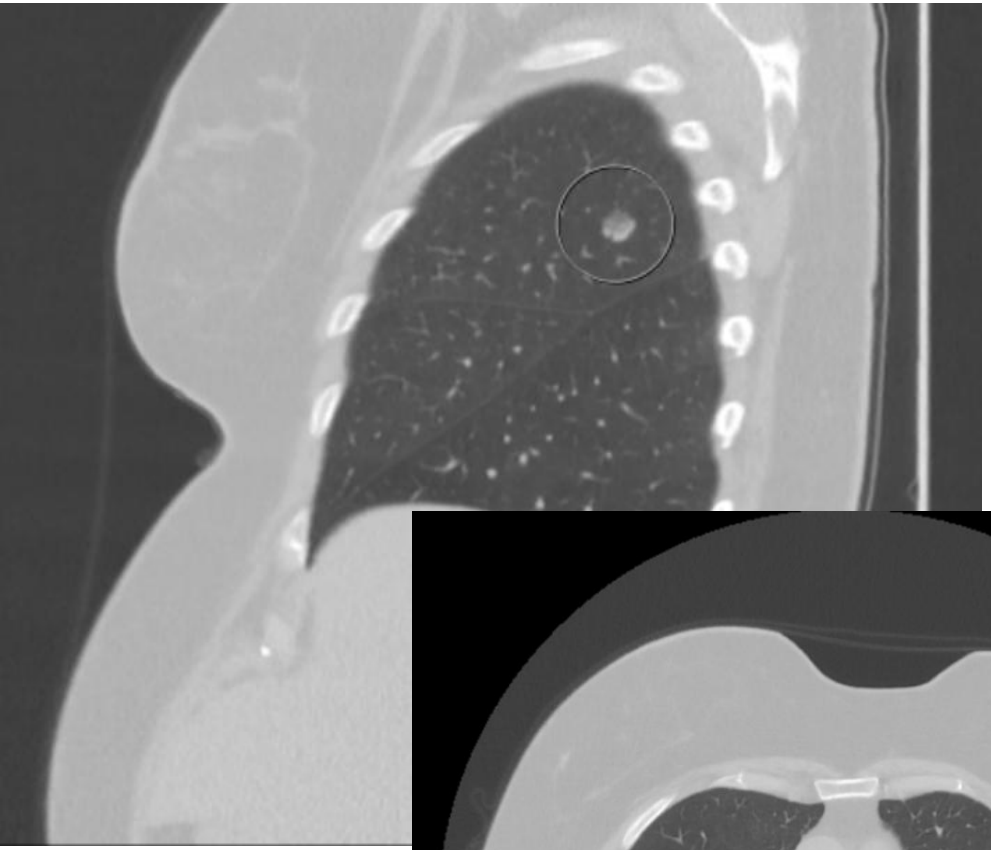


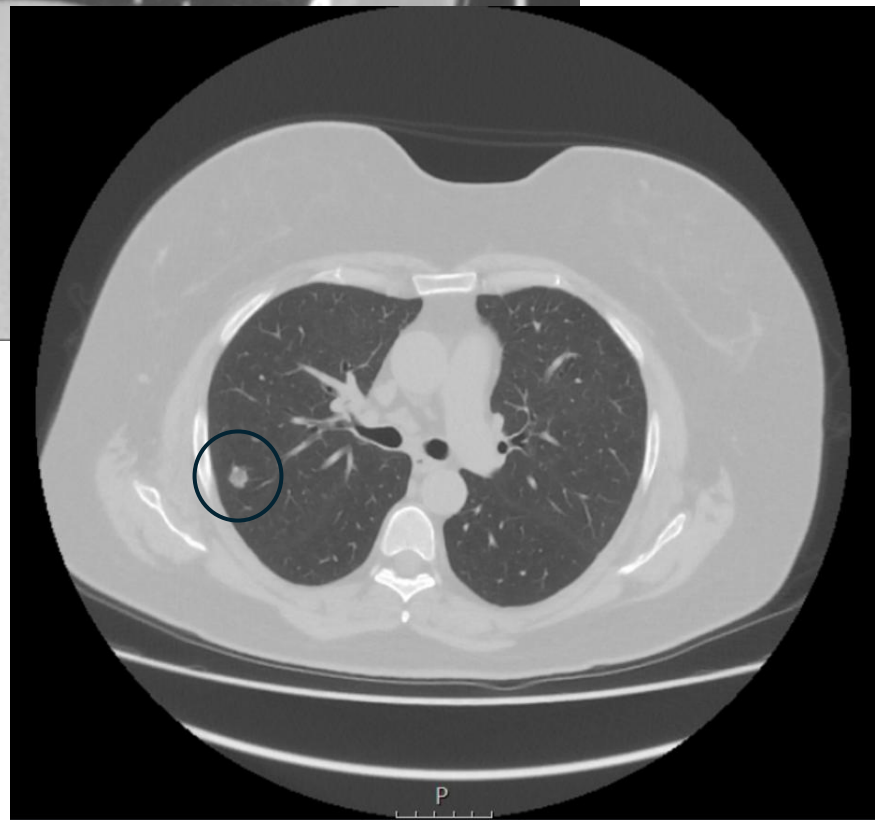
Interpreting broad-panel NGS

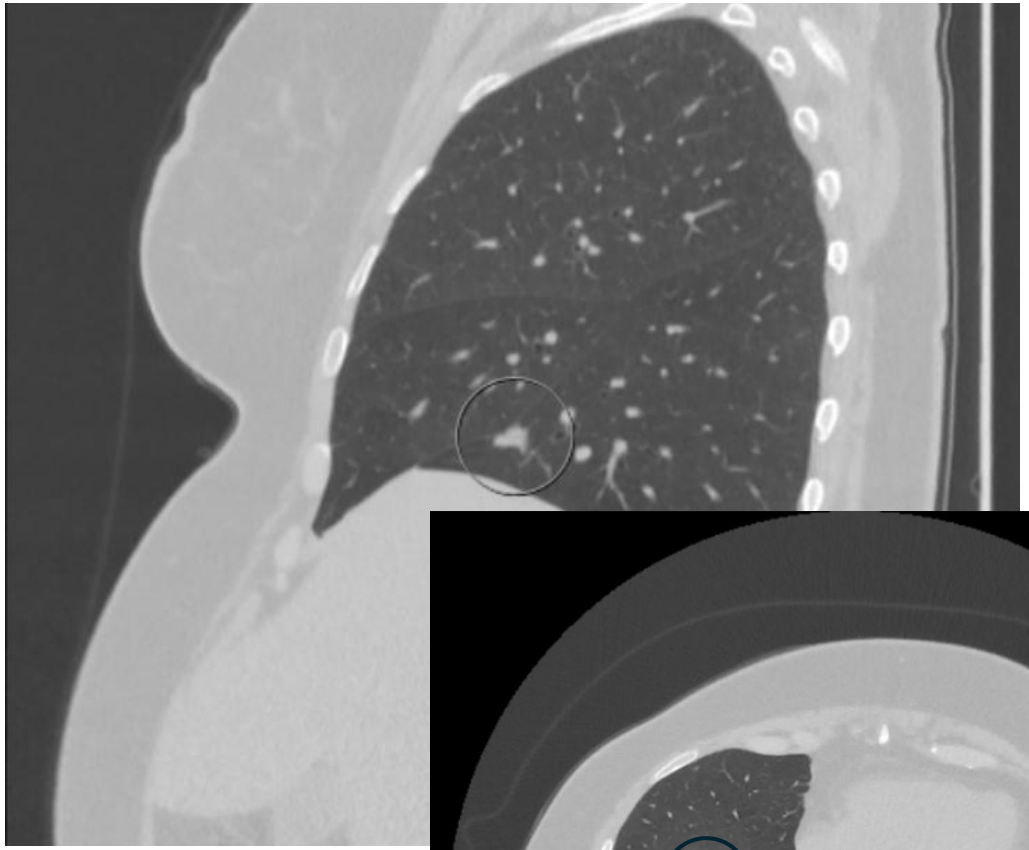
Mutation A Mutation B Mutation C Mutation D	Mutation E Mutation F Mutation G Mutation H	SPLC
Common Driver A Mutation B Mutation C Mutation D	Common Driver A Mutation F Mutation G Mutation H	SPLC
Mutation A Mutation B Mutation C Mutation D	Mutation A Mutation B Mutation C Mutation D	IPM#

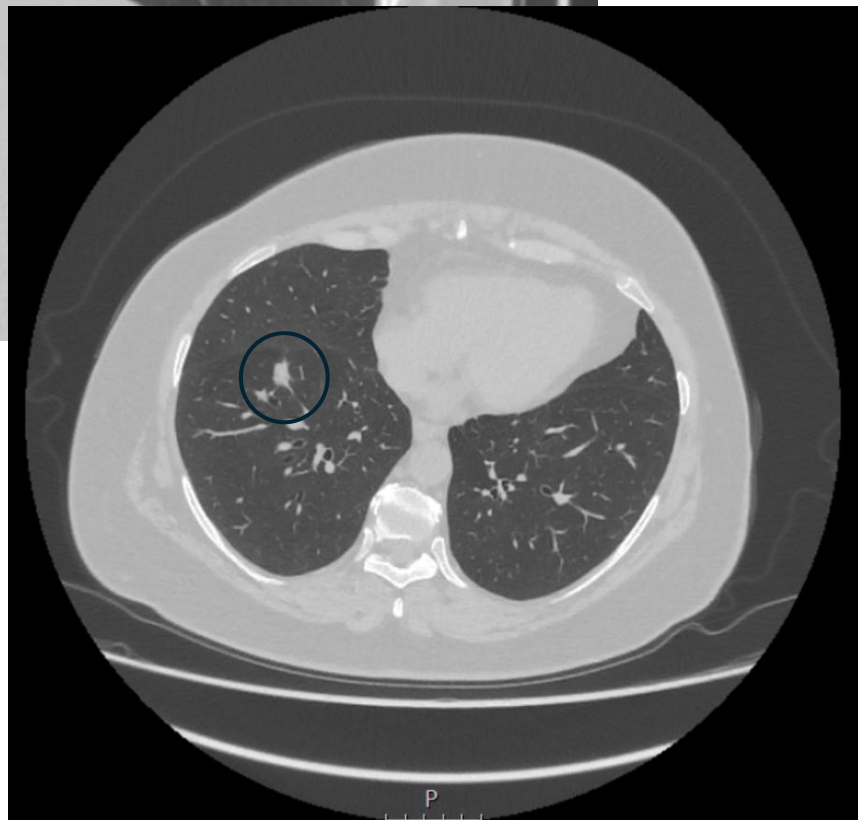
#Can have unique mutations due to clonal evolution, but shared mutations typically outnumber unique mutations in NSCLC IPMs

65 yo woman, current smoker, two tumors detected (RUL, RLL) through CT screening study

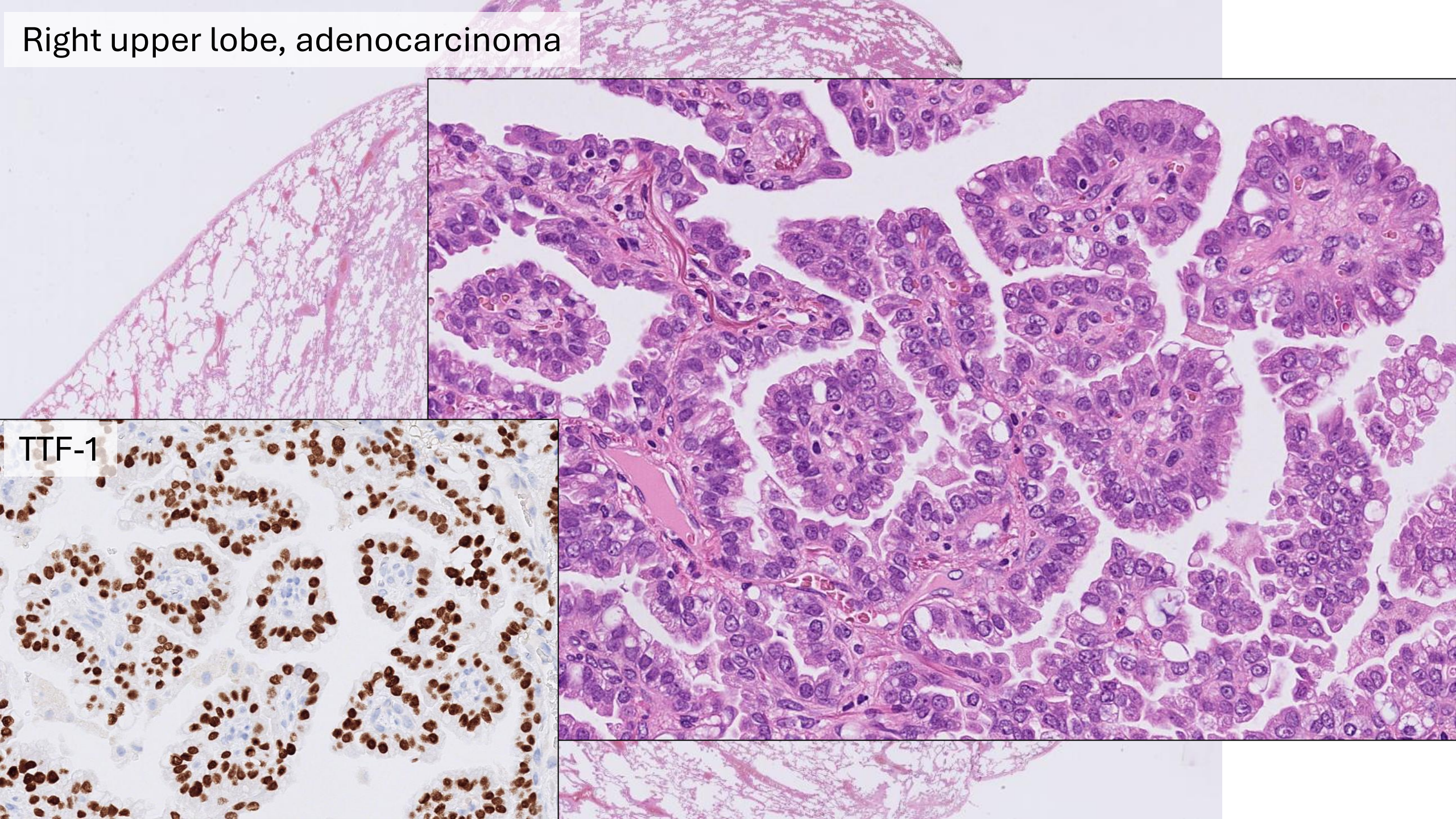






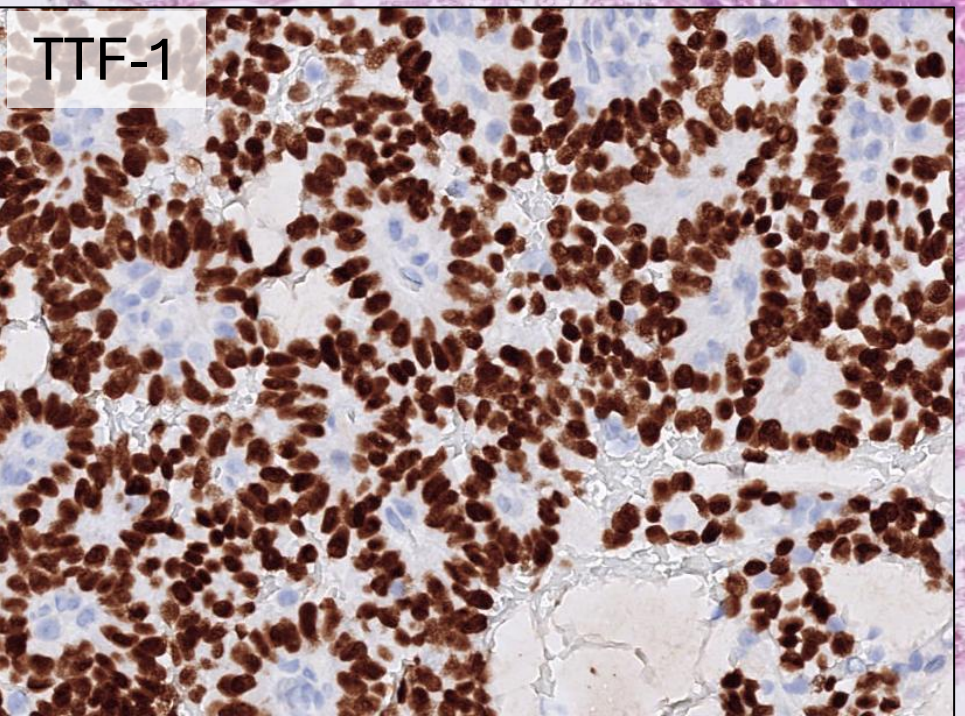


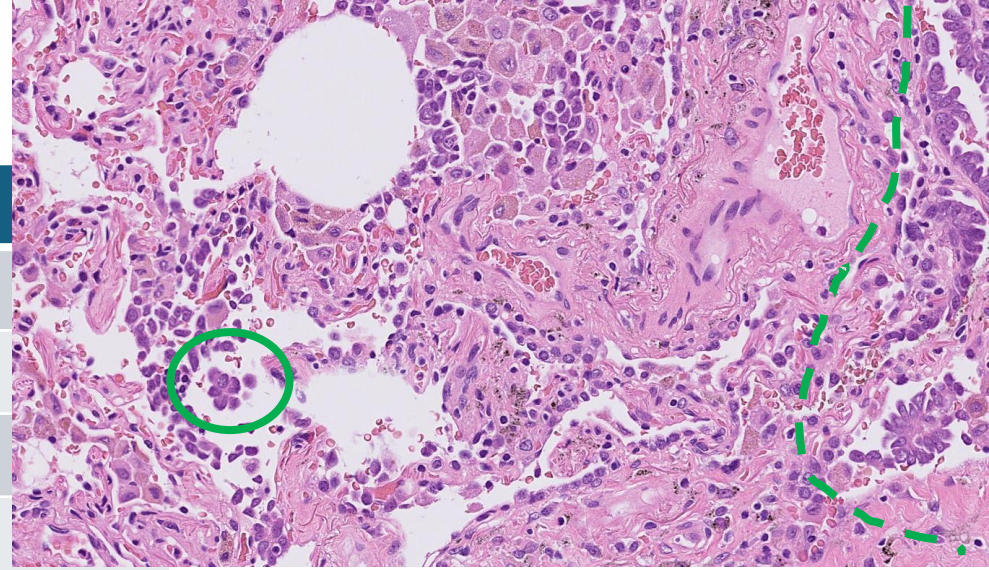
Right upper lobe, adenocarcinoma



TTF-1

Right lower lobe, adenocarcinoma





Tumor 1 (upper lobe)	Tumor 2 (lower lobe)
Adenocarcinoma	Adenocarcinoma
Papillary	Papillary and acinary
TTF-1 +	TTF-1 +
1.4 cm	1.2 cm
	Spreading through airspaces (STAS)
No pleural involvement	No pleural involvement (but uncertain)
No lymph node involvement	

pT1b + pT1b (I A) *or* pT4 (IIIA)?

Oncomine Focus, Thermo Fisher Scientific

Tumor 1 (upper lobe)	Tumor 2 (lower lobe)
KRAS G12C (34G>T) 22%	KRAS G12C (34G>T) 23%
	CTNNB1 S33C (98C>G) 15%

GMS560, Genomics Medicine Sweden

Tumor 1 (upper lobe)	Tumor 2 (lower lobe)
KRAS G12C 20%	KRAS G12C 22%
KEAP 25%	
STK11 28%	
AURKC 20%	
WT1 18%	
SMC1A 21%	
AKT2 20%	
IGF1R 9%	
APC 17%	
GRIN2D 23%	
	CTNNB1 13%
	BCOR 21%
	CDH1 21%
	DMD 3%

The LCNEC problem

TLCR Translational Lung Cancer Research
An open access journal focusing on closing the gap between "bench and bedside"
4 Impact Factor | 7.2 CiteScore

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diagnostics

MDPI

tive Biomarkers of Lung Cancer

rcinoma

Review

A Novel Strategy for the Diagnosis of Pulmonary High-Grade Neuroendocrine Tumor

Kentaro Miura [1], Kimihiro Shimizu [1,*], Shogo I
Takashi Eguchi [1], Kazutoshi Hamanaka [1] and

IASLC

STATE OF THE ART: CONCISE REVIEW

Clinical-Pathologic Challenges in the Classification of Pulmonary Neuroendocrine Neoplasms and on for Future Clinical Practice

Check for updates

ole Rijnsburger, MSc,[b,c] Bregtje C. M. Hermans, MD,[a]
lillen, MD, PhD,[d] Jan H. von der Thüsen, MD, PhD,[c]
D,[e] Robert J. van Suylen, MD, PhD,[f]
e-Marie C. Dingemans, MD, PhD[a,b]

Pathology & Oncology Research

frontiers

REVIEW
published: 11 October 2022
doi: 10.3389/pore.2022.1610730

Check for updates

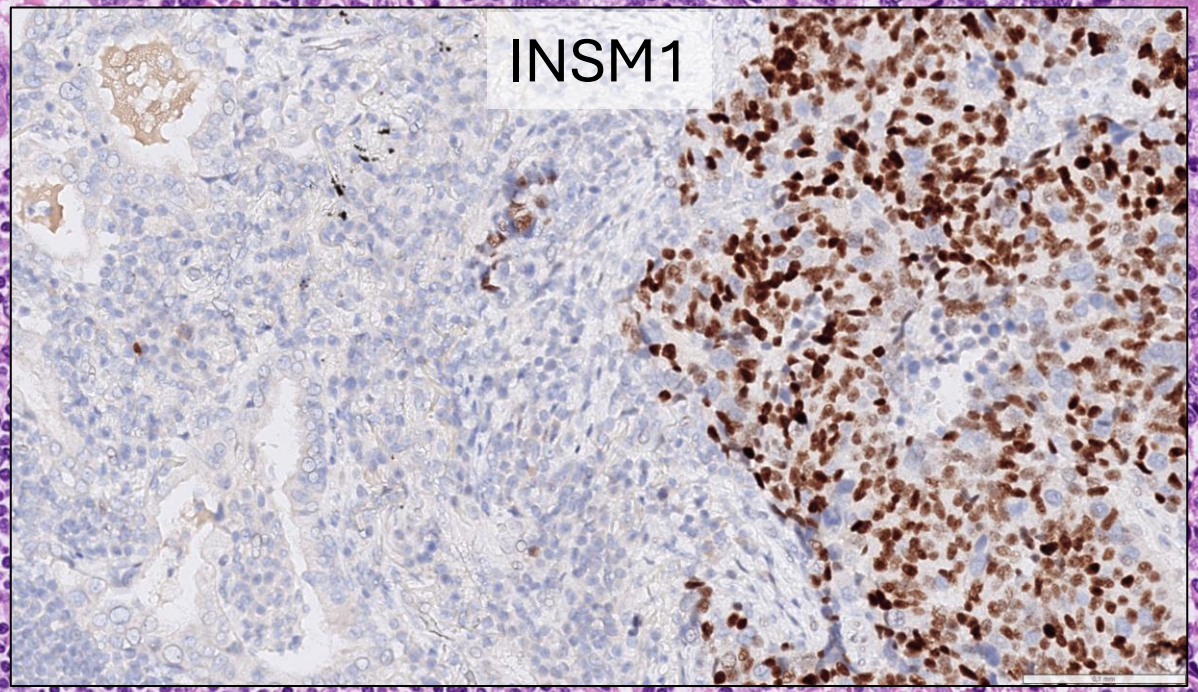
Pulmonary Large Cell Neuroendocrine Carcinoma

Lan Yang[1,2,3,4†], Ying Fan[1,2,3,4†] and Hongyang Lu[1,2,3,4]*

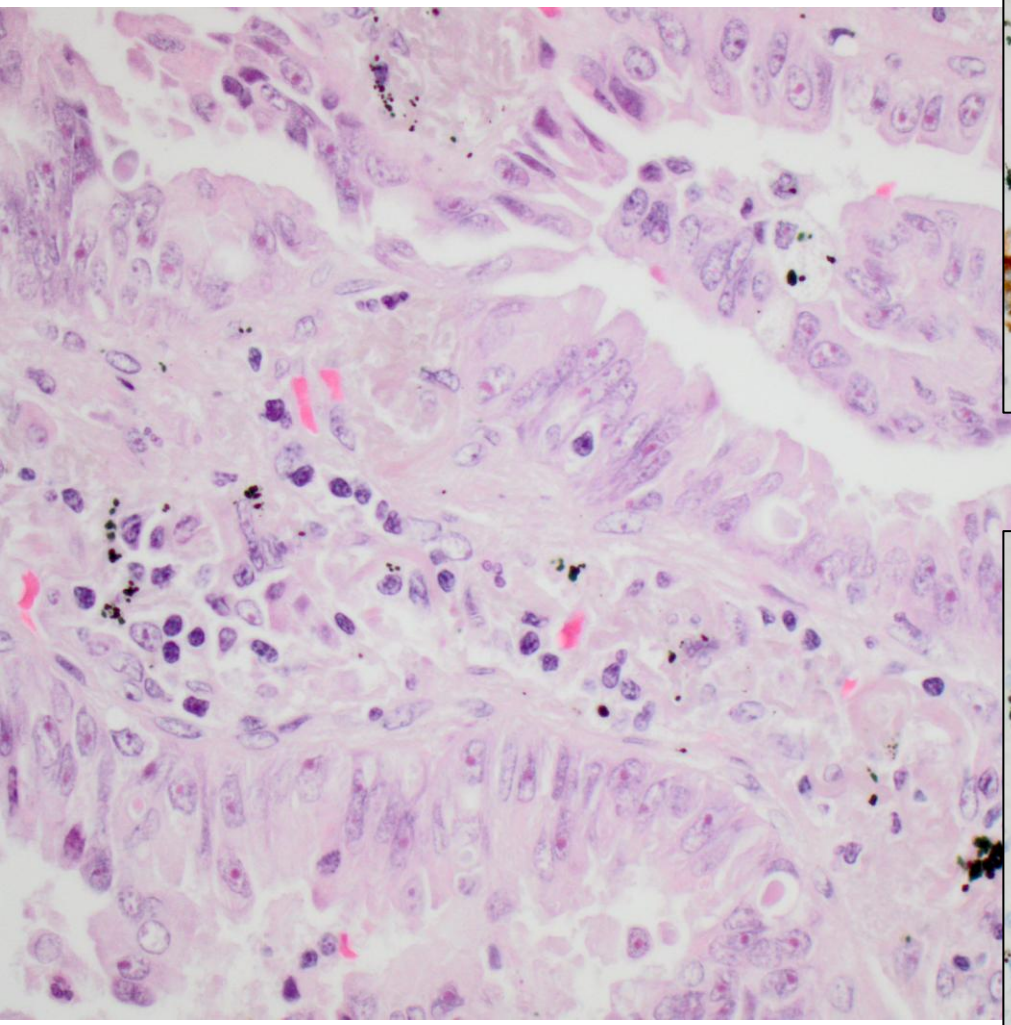
Staining	LCNEC	Adenocarcinoma
Mucin inclusions	None to occasional	None to many
TTF-1	+/-	+/(-)
Napsin A	-/(+)	+/(-)
Neuroendocrine markers	+/(-)	-/(+)
Ki67	Typically moderate to high	Typically low to moderate
Rb1	Sometimes lost	Preserved
p16	+/-	-/(+) (if high cutoff)

Overlapping IHC profiles – diagnostics relies on morphology

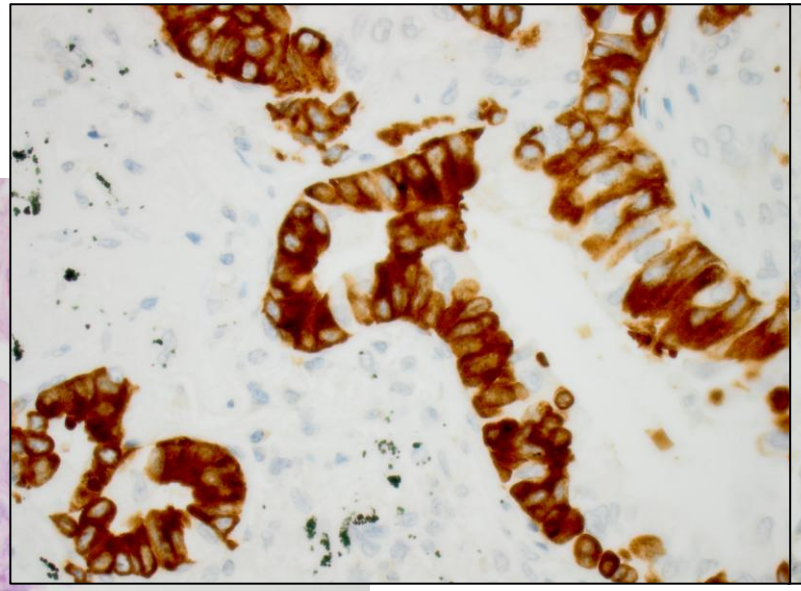
Combined LCNEC and adenocarcinoma



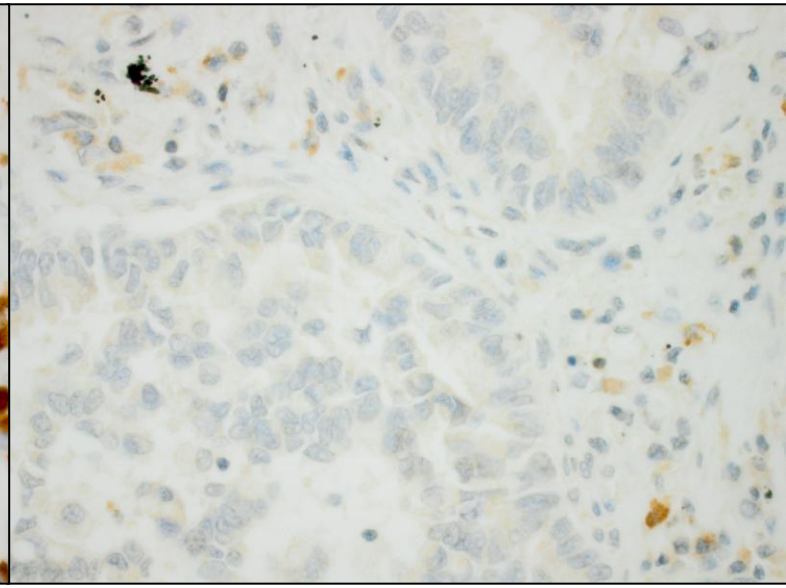
Adenocarcinoma



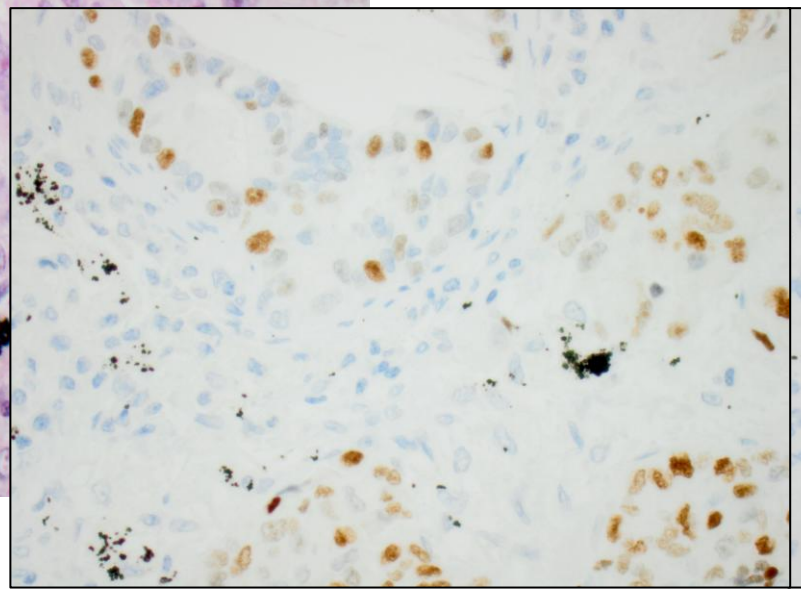
Synaptophysin



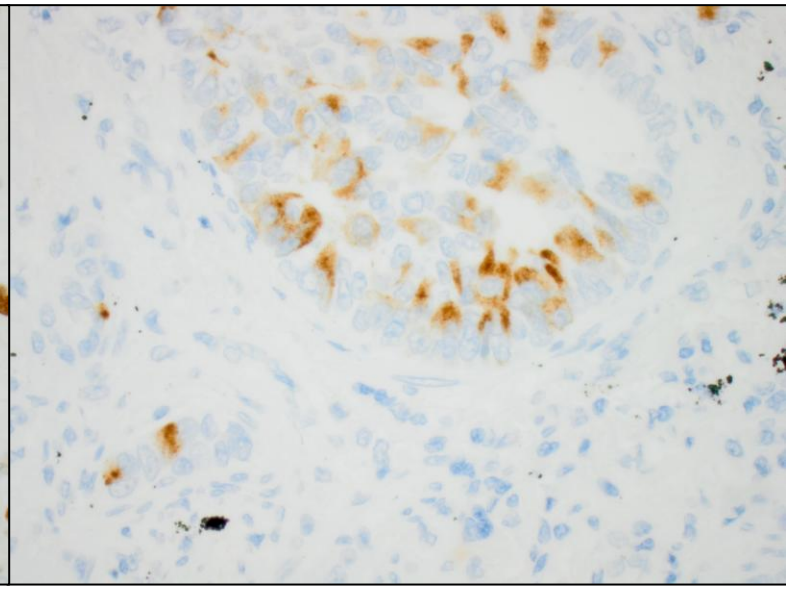
CD56



INSM1



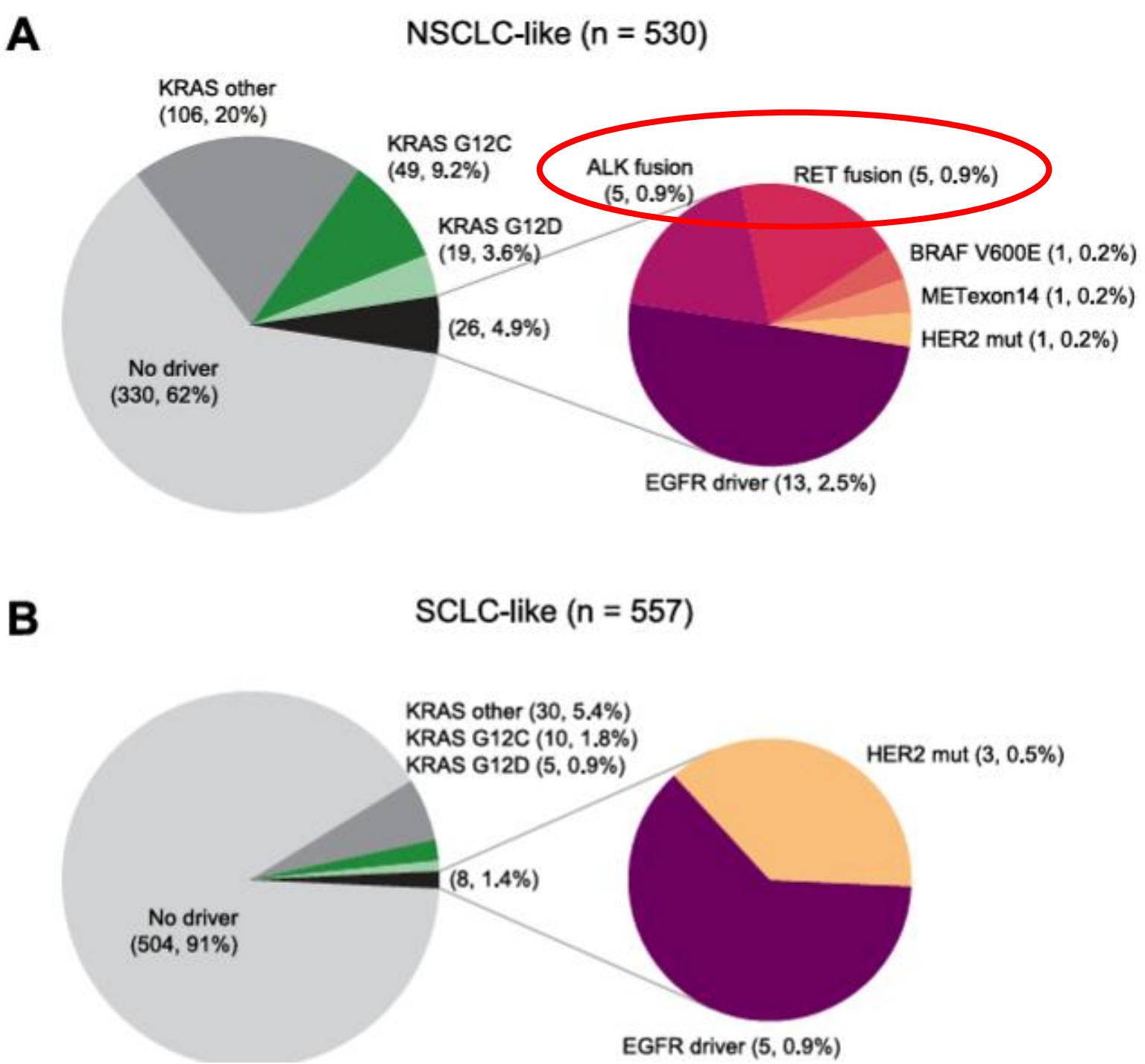
Chromogranin A



LCNEC

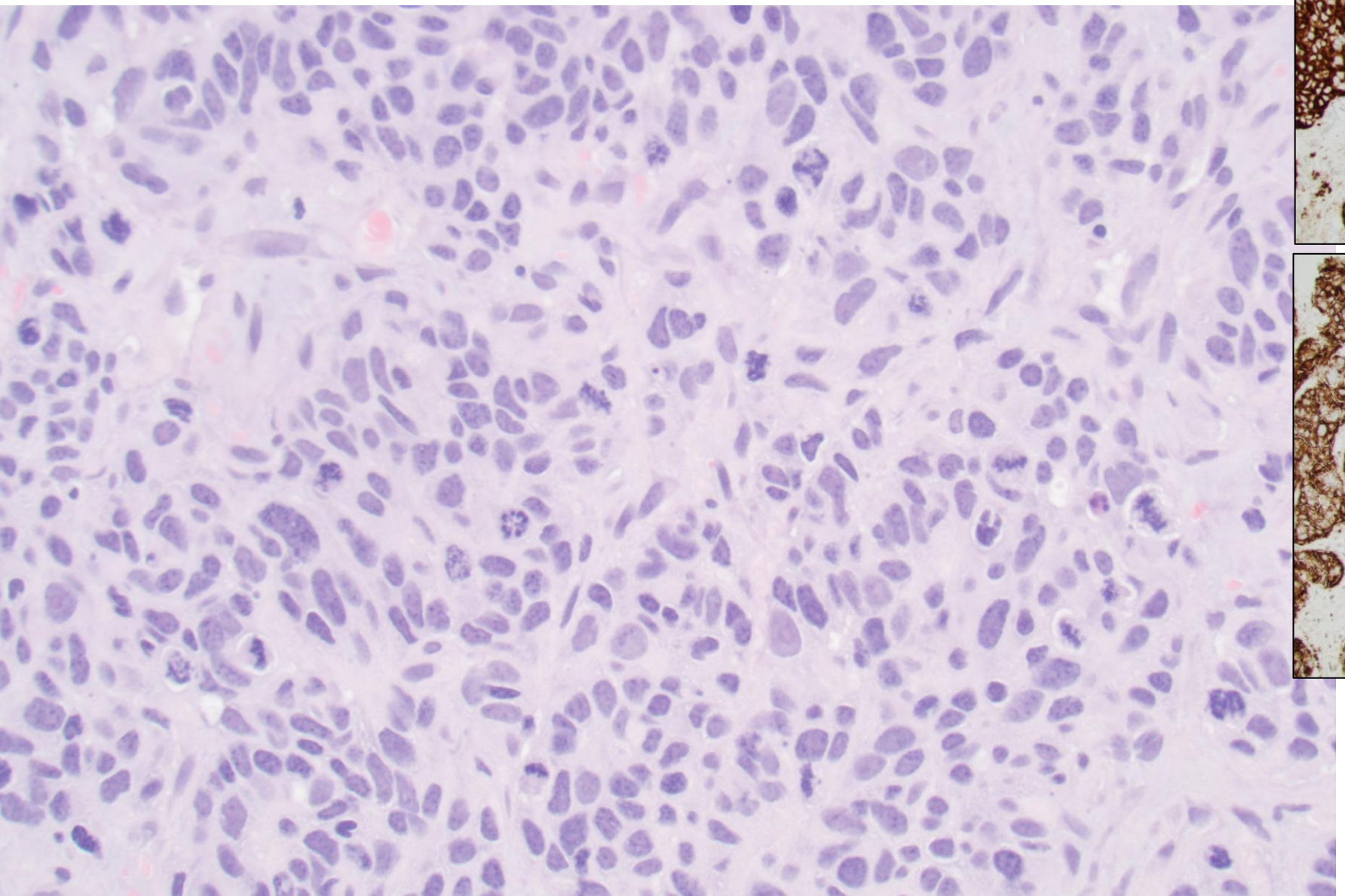
Genes Class defining	SCLC -like (557)	NSCLC -like (530)	Carcinoid -like (25)	Unclassified (314)
RB1	100%	3.2%	0%	4.5%
TP53	100%	71.3%	0%	58.3%
MEN1	0.4%	0%	100%	1.3%
CDKN2A/B/MTAP	3.4%	41.5%	8.0%	0%
STK11	5.7%	39.8%	0%	0%
KRAS	7.9%	32.3%	0%	0%
SMARCA4	3.2%	18.5%	0%	0%
FGF3/4/19/CCND1	0.7%	13.0%	0%	0%
Non-KRAS driver	1.4%	4.9%	0%	0%

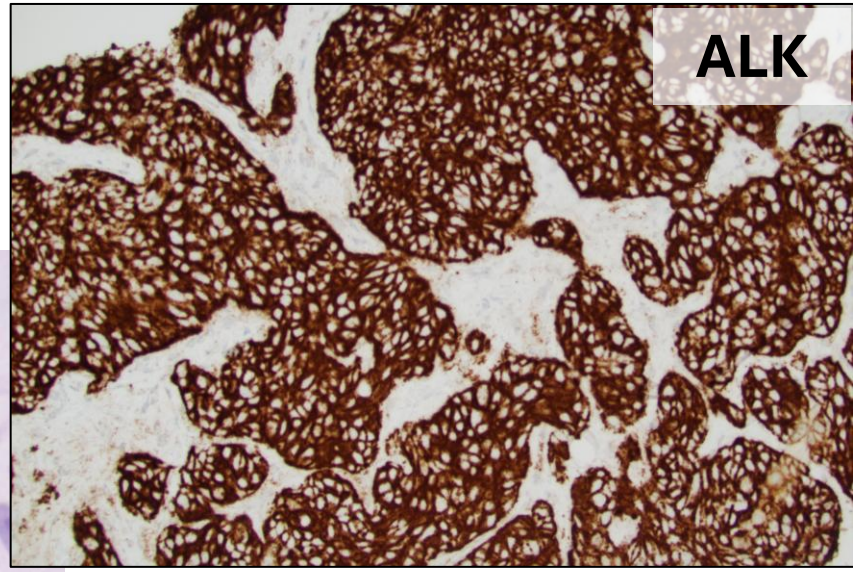
PMID: 38159439

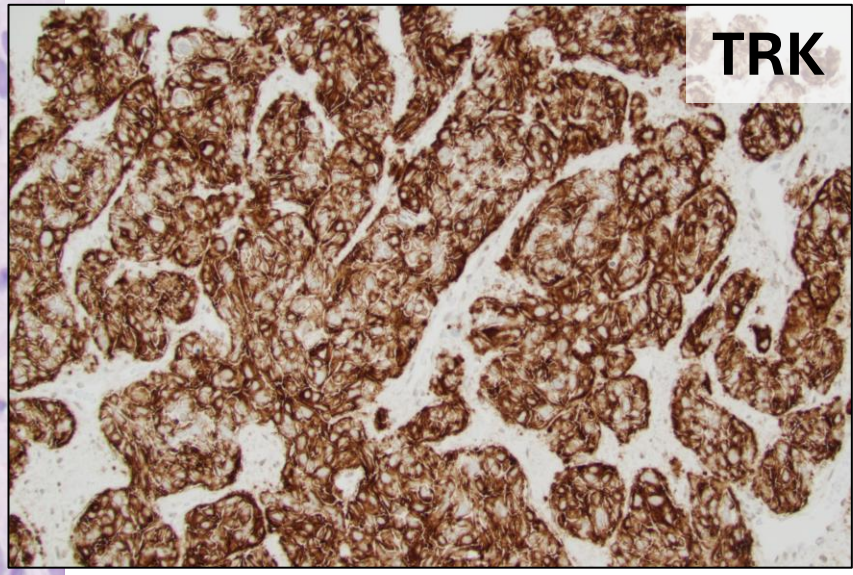


PMID: 38159439

LCNEC with positive ALK and NTRK immunostain but no fusions







Detected mutations:
RB1, TP53

Summary

Molecular testing in lung cancer

- Predictive
  - stage IB-IV
  - NSCC, uncertain types, and (at least NSCC-like) LCNEC
- TKI resistance
- Diagnostic
  - Type-specific alterations
  - Profiling for staging/multiple lung cancers