

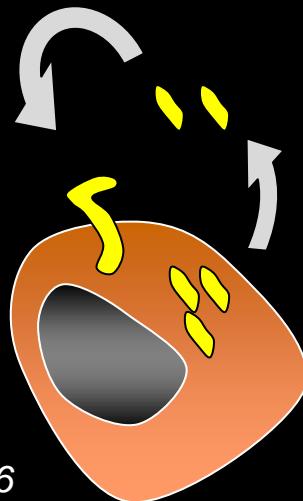


Translational lung cancer research: The Uppsala approach

Johan Botling, Patrick Micke

From basic science to clinical practice or vice versa?

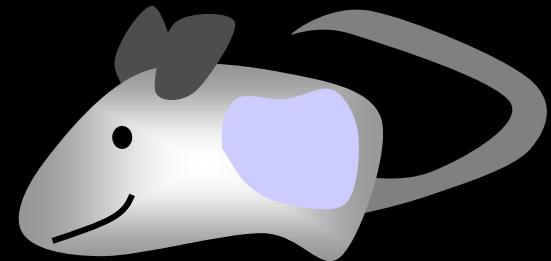
KIT



SCLC cell line

in vivo experiments

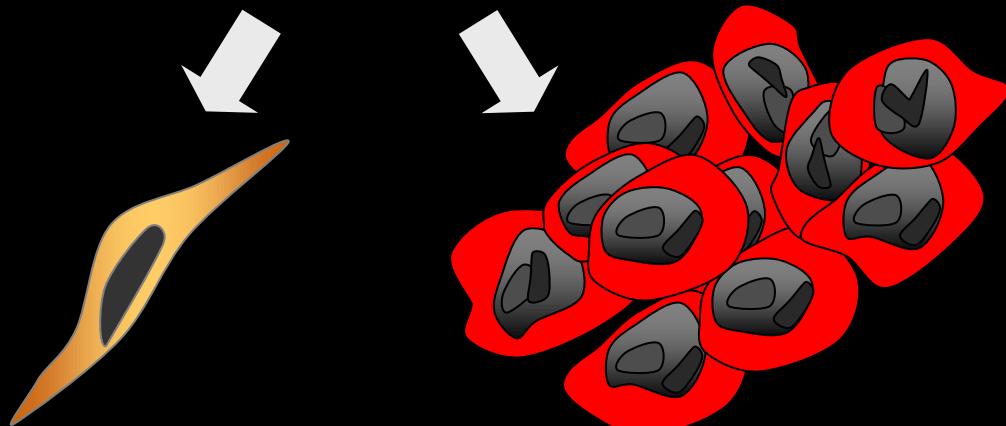
KIT



Krystal et al.
Cancer Res, 1996

in vitro experiments

KIT overexpression



CKIT is relevant in SCLC
CKIT is a target

?

Phase II study of Imatinib in extensive SCLC

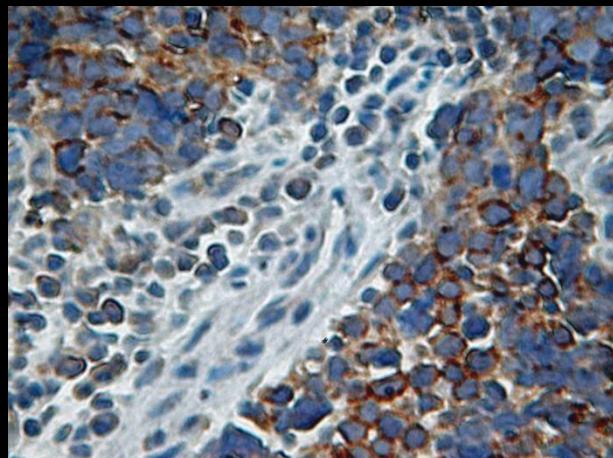


Johnsen , Fischer et al., 2003 Clin Cancer Res

No objective response

Progression free survival : 1 month

Overall survival: 8 month



CKIT is expressed in SCLC IHC: 30%
no mutations
no amplification

Micke et al., 2003 Clin Cancer Res
Burger et al., 2003 Eur J Cancer

Raise standards for preclinical cancer research

C. Glenn Begley and Lee M. Ellis propose how methods, publications and incentives must change if patients are to benefit.

“ Many landmark findings in preclinical oncology research are not reproducible, in part because of inadequate cell lines and animal models.”

“ Some non-reproducible preclinical papers had spawned an entire field with hundreds of secondary publications....”

Translational cancer research

tumor samples / biobank

clinical data / cancer registry

molecular analysis platforms



3619.L1 T

3625.L1 LN

3619.L2 N

* 3620.2.1

3621.L.1

3621.L.2

3622.L.1 T

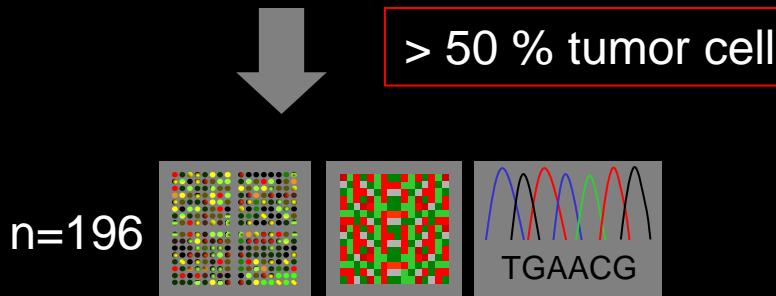
3625.L1 T



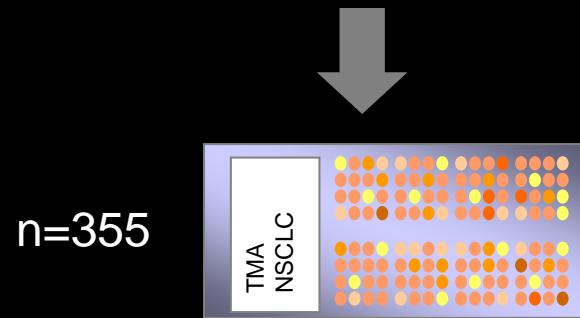
Molecular profiling of NSCLC

Uppsala Lung Cancer Network

398 operated cases (1995-2005) with fresh frozen tissue



66 squamous cell carcinoma
106 adenocarcinoma
24 large cell carcinoma

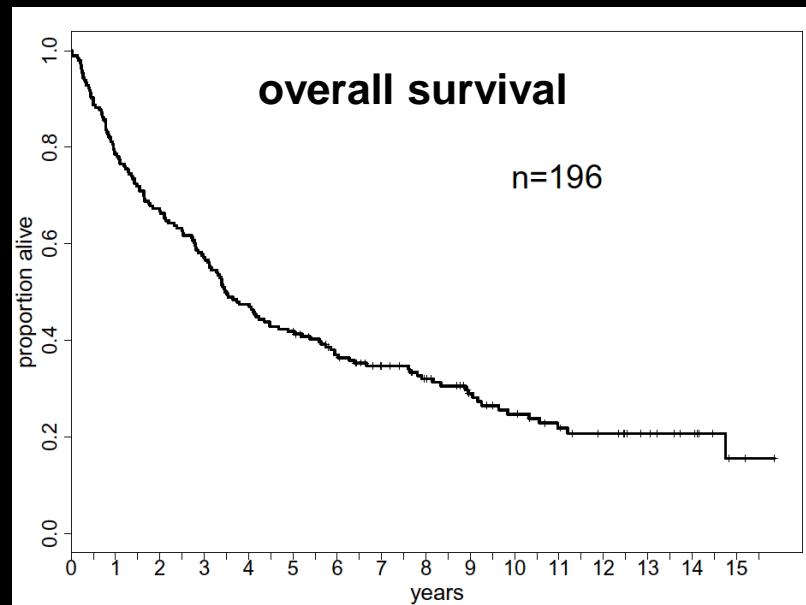


Clinical database:

- age
- gender
- smoking status
- performance status
- stage
- survival

KRAS
mutated: 49
wildtype: 147

EGFR
mutated: 25
wildtype: 171



Global gene expression analysis

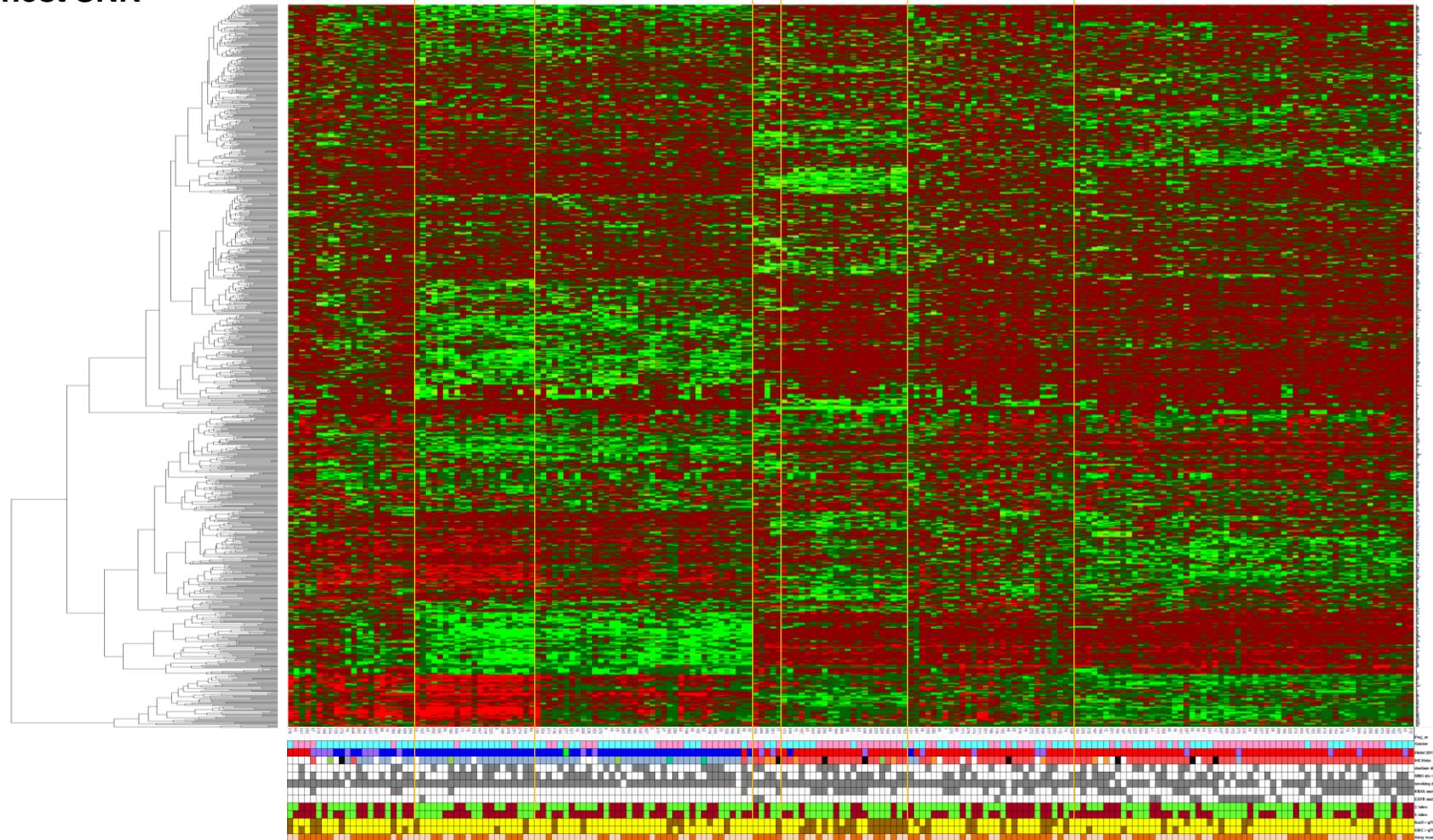
Hierarchical clustering

all patients

n = 196

top 1000 genes

highest SNR



Gene expression in NSCLC

- many, mostly relative small cohorts (50-100) or pooled data.
- mostly adenocarcinoma
- inclusion of same cohorts in different studies (e.g. Beer study)
- often only survival, gender, age and histology
- prognostic signatures from five to 100 genes, few overlap
- biological relevance?
- high impact publications (nature medicine, J Clin Oncol, JNCI, Lancet)

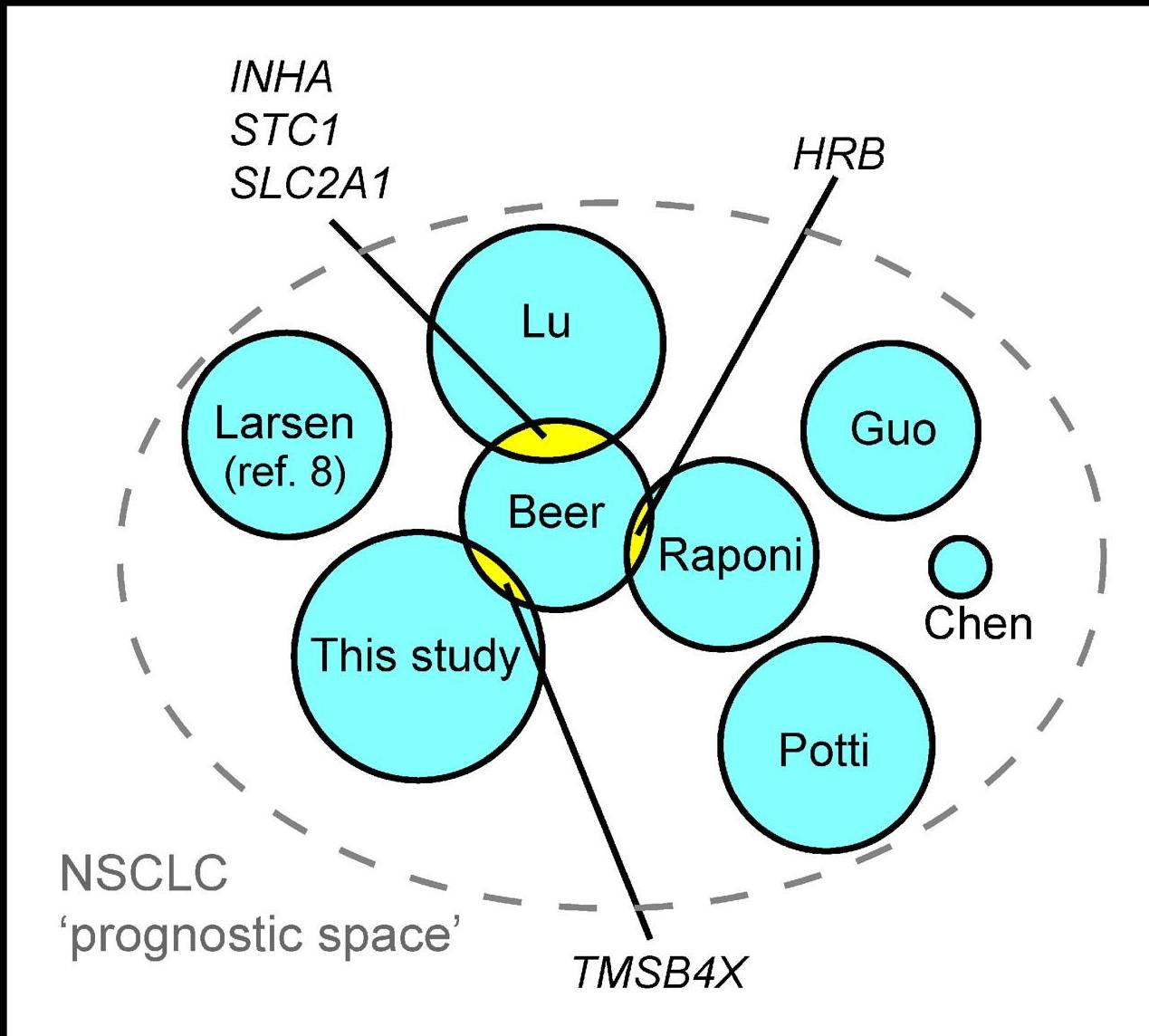
Gene Expression-Based Prognostic Signatures in Lung Cancer: Ready for Clinical Use?

JNCI 2010

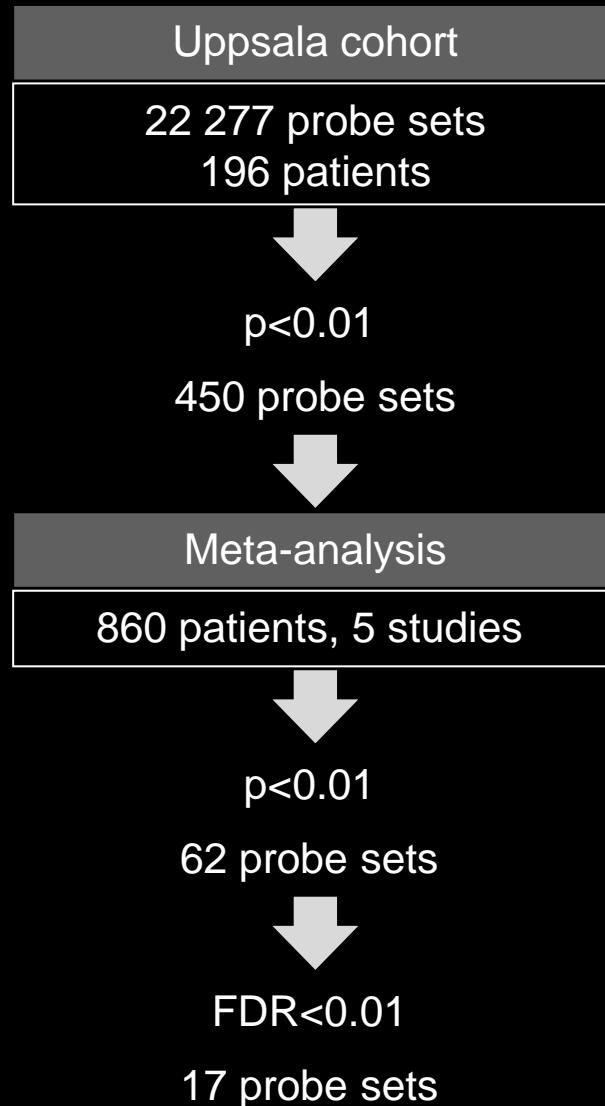
Jyothi Subramanian, Richard Simon

- Gene signatures do not outperform traditional clinical parameters...
- Gene signatures do not add biological information...

Overlap of prognostic gene signatures



Prognostic signatures in the Uppsala cohort



Jan Hengstler IfADo

Jörg Rahnenführer TU Dortmund

A meta-analysis approach to identify clinically relevant biomarkers

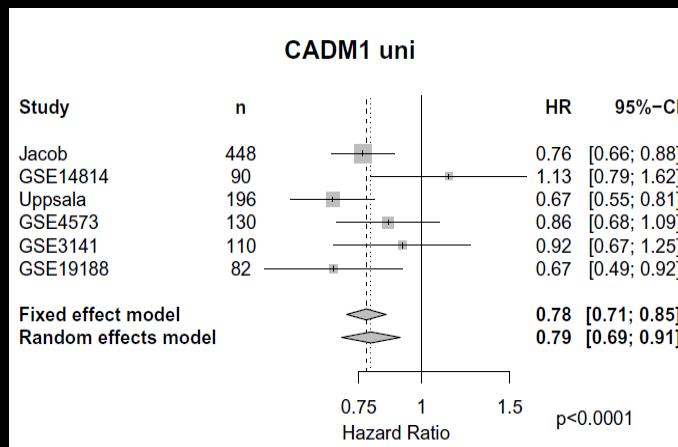
Prognostic genes in Uppsala NSCLC p<0.01 and
1% false discovery rate in the meta-analysis

n =196 n =860

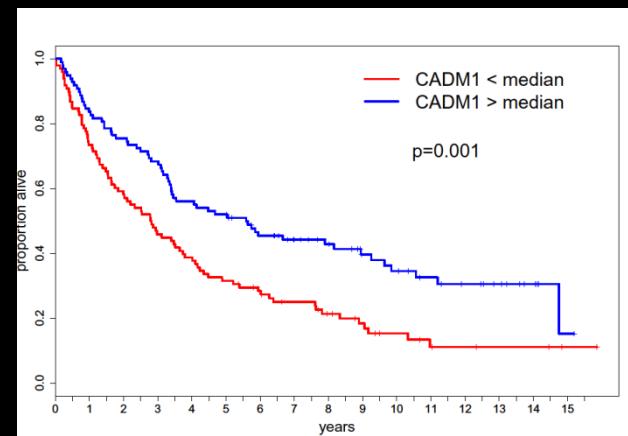
Affy ID	symbol	gene name	p Uppsala	p meta-analysis
201037_at	PFKP	phosphofructokinase, platelet	0.001337	0,000004
202524_s_at	SPOCK2	sparc/osteonectin, cwcv and kazal-like domains proteoglycan 2	0.002343	0.000174
202616_s_at	MECP2	methyl CpG binding protein 2 (Rett syndrome)	0.007879	6.6e-05
204385_at	KYNU	kynureninase (L-kynurenone hydrolase)	0.005011	0,000000
205839_s_at	BZRAP1	benzodiazapine receptor (peripheral) associated protein 1	0.009713	0,000008
206571_s_at	MAP4K4	mitogen-activated protein kinase kinase kinase kinase 4	0.000623	0.000321
209030_s_at	CADM1	cell adhesion molecule 1	8.9e-05	3.6e-05
209031_at	CADM1	cell adhesion molecule 1	5.2e-05	8.9e-05
209032_s_at	CADM1	cell adhesion molecule 1	6.8e-05	6.4e-05
210663_s_at	KYNU	kynureninase (L-kynurenone hydrolase)	0.003762	0,000010

A meta-analysis approach to identify clinically relevant biomarkers

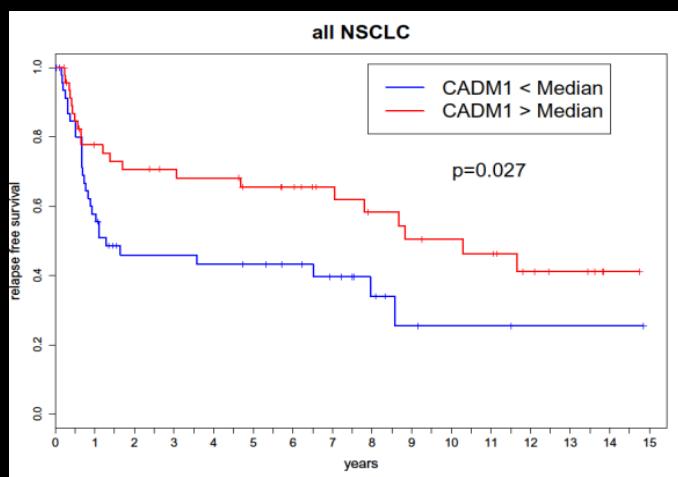
meta-analysis



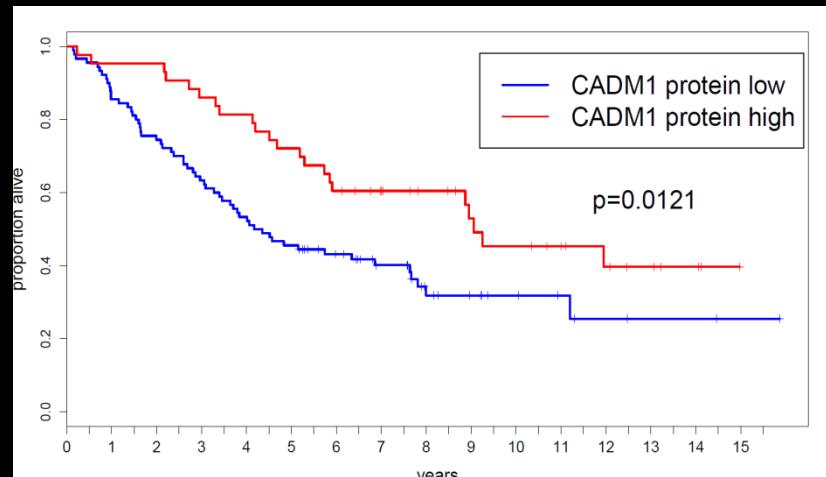
overall survival



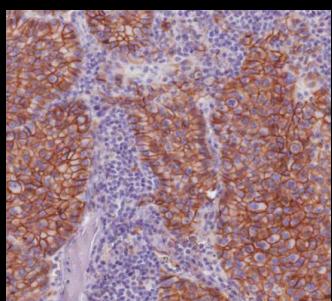
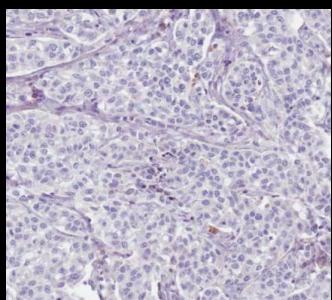
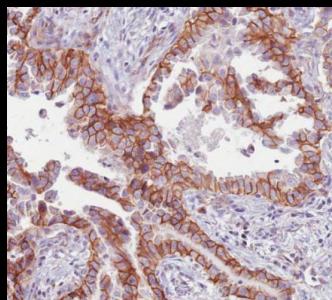
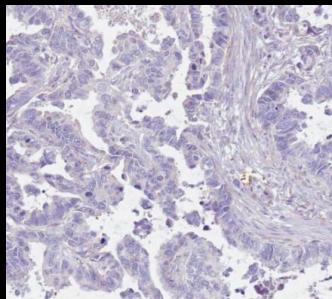
recurrence free survival



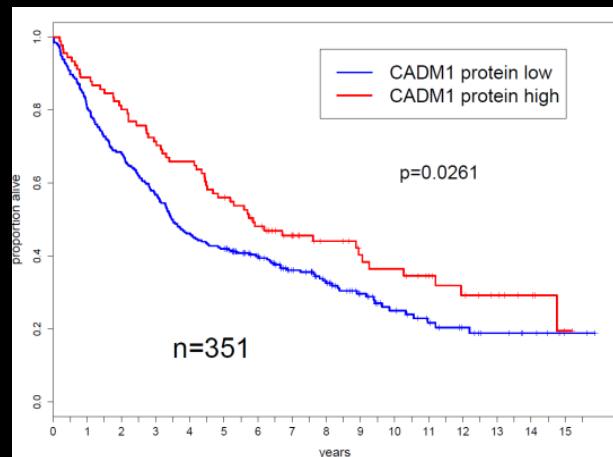
stage I patients



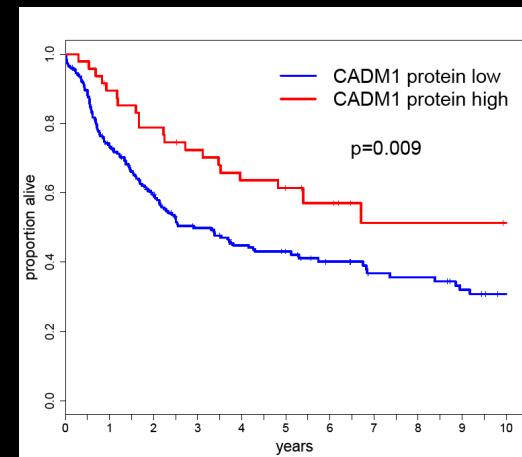
CADM1 protein expression as a prognostic biomarker



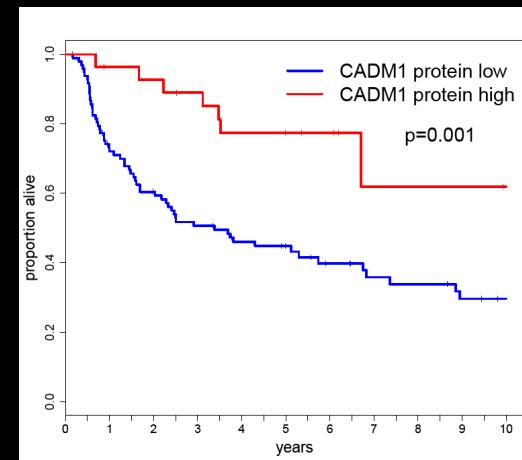
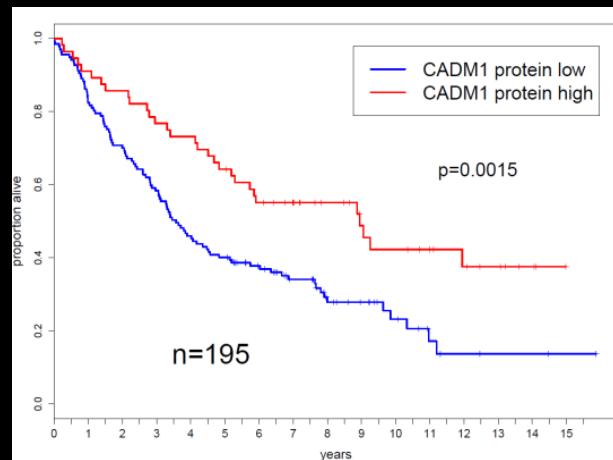
Uppsala cohort, n=351



Örebro cohort, n=261

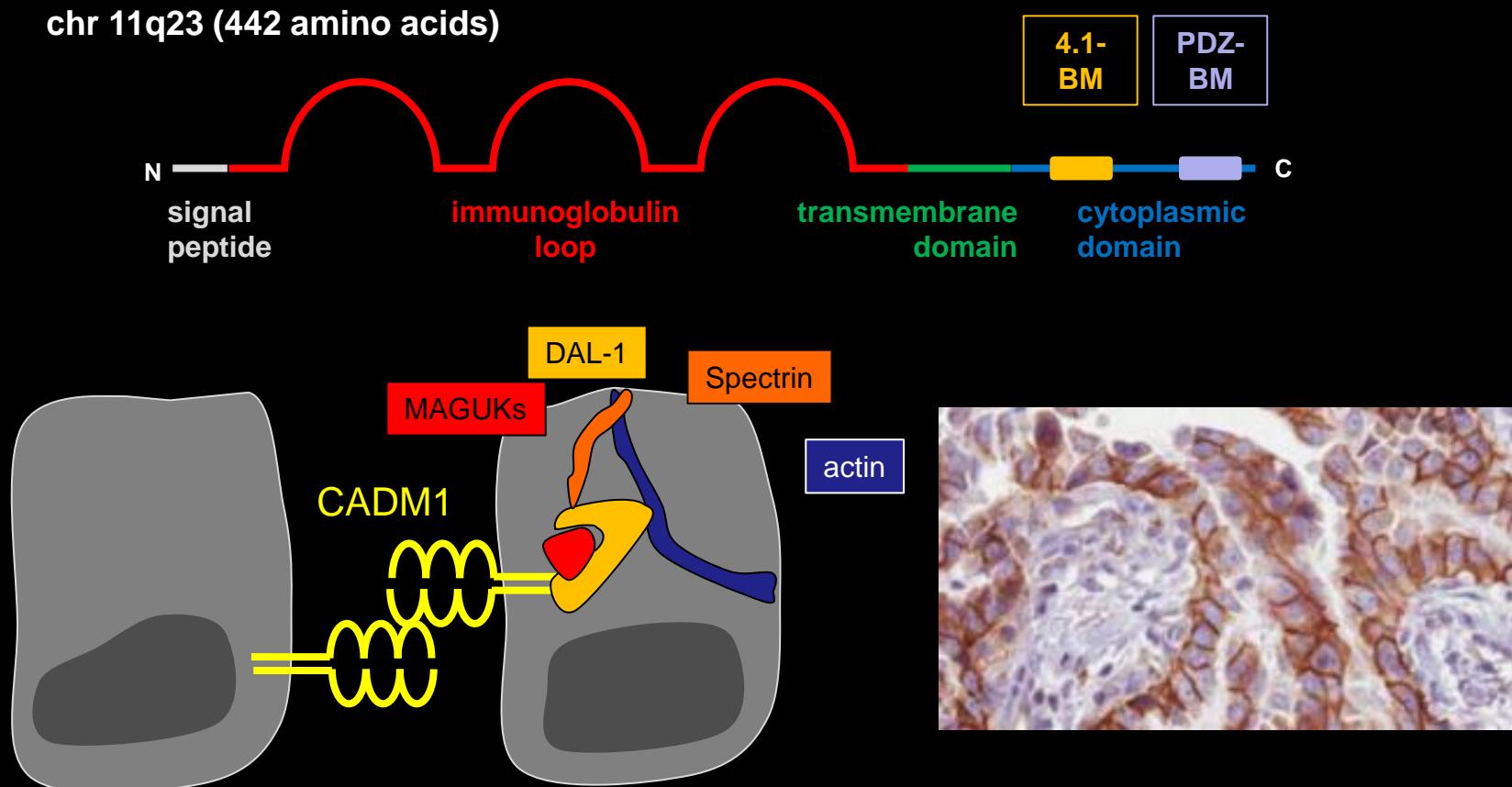


adenocarcinoma

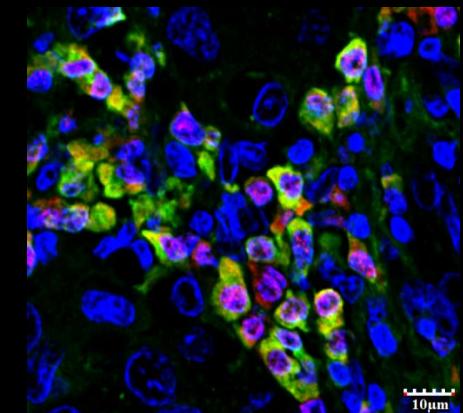
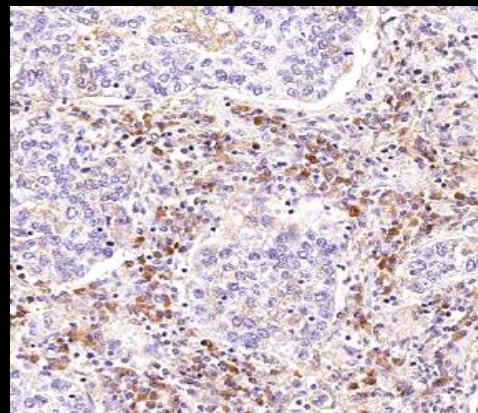
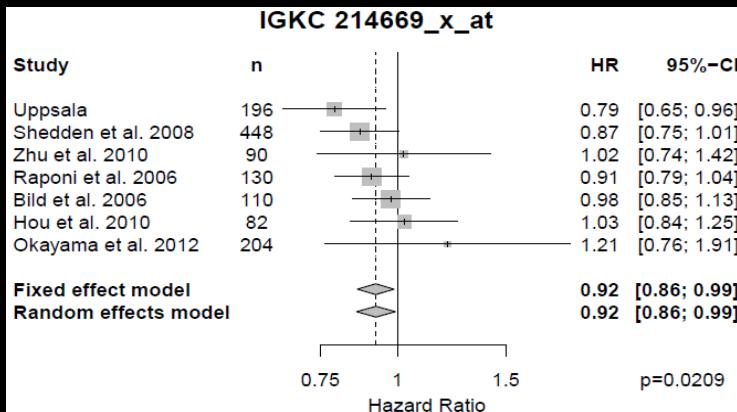


CADM1 (cell adhesion molceule 1) in NSCLC

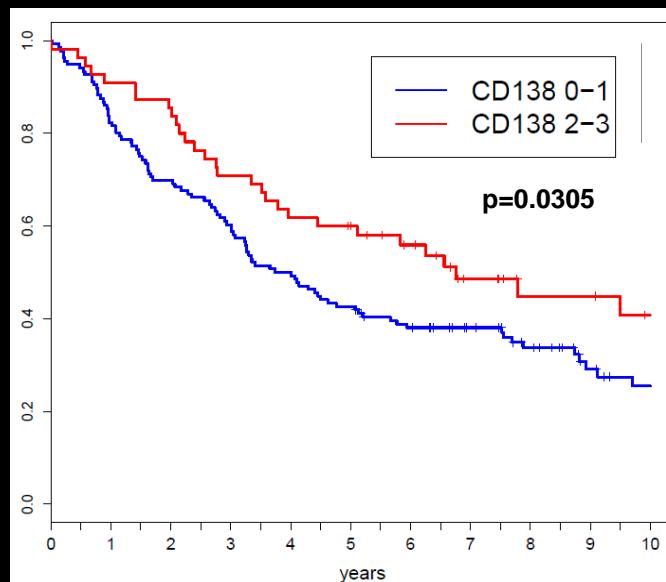
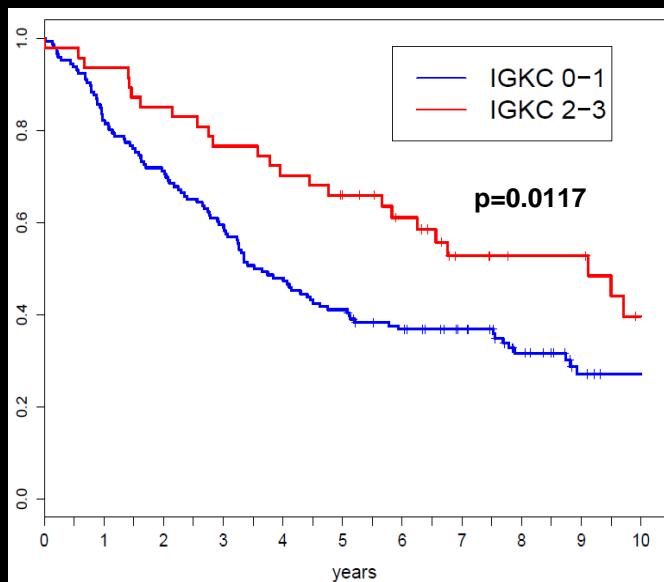
Synonyms: TSCLC1 (Tumor suppressor in lung cancer 1)
IGSF4 (immunoglobulin superfamily member 4)



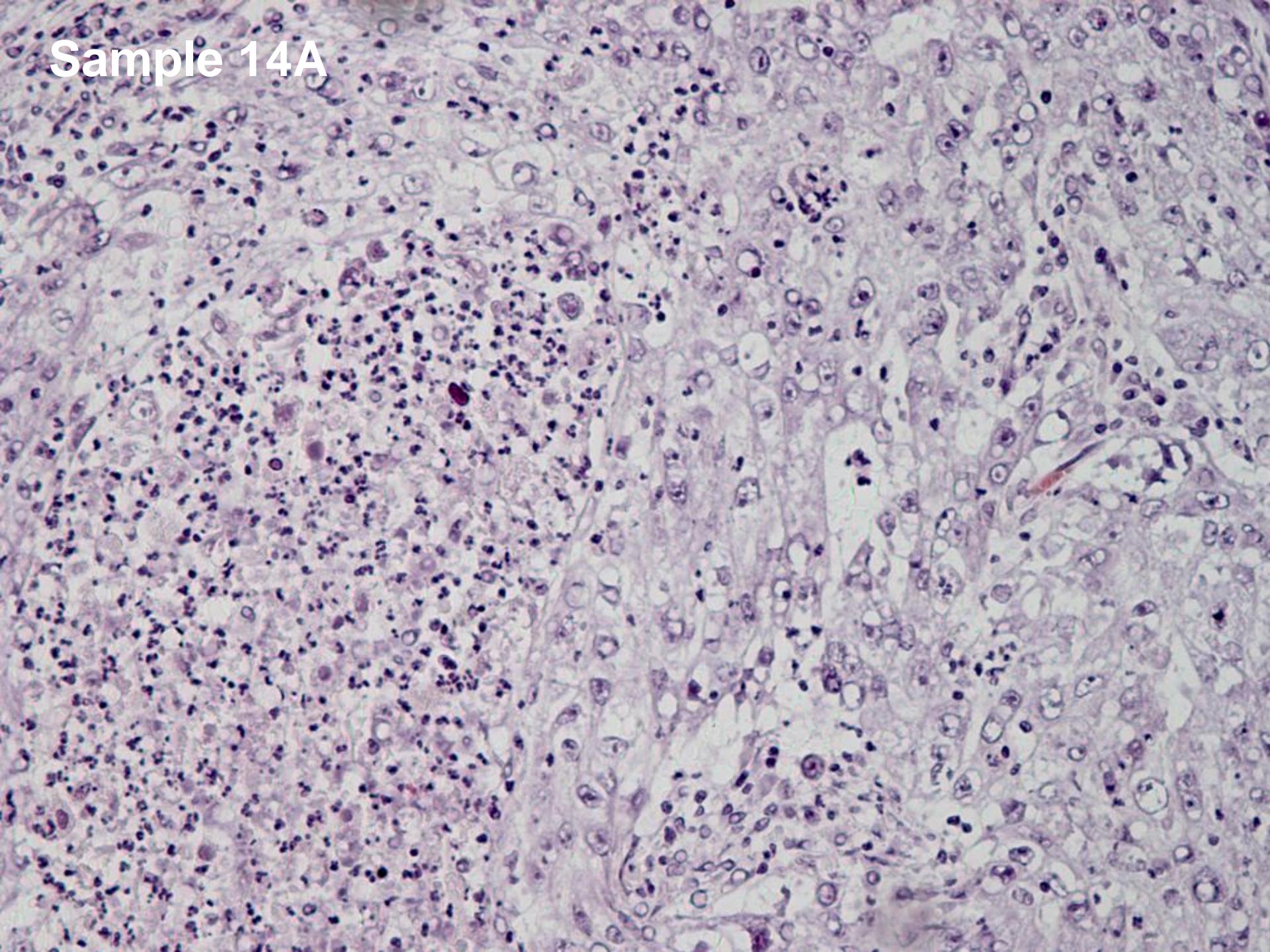
Stromal IGKC / intra tumoral plasma cell infiltration in NSCLC



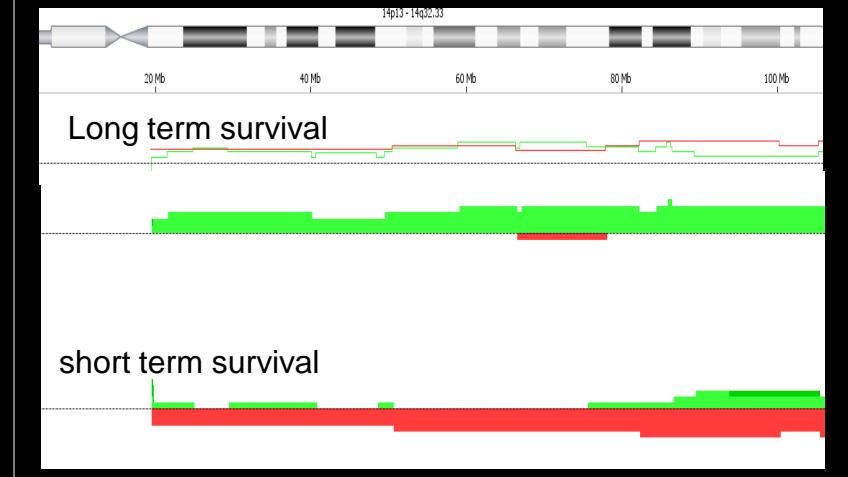
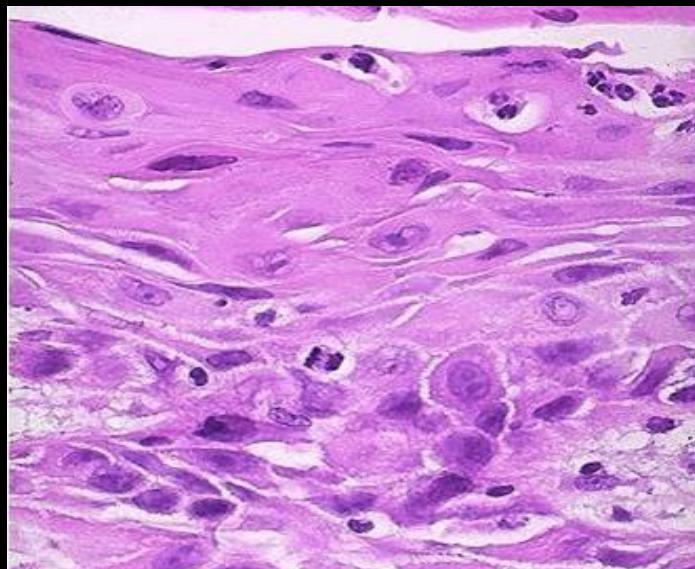
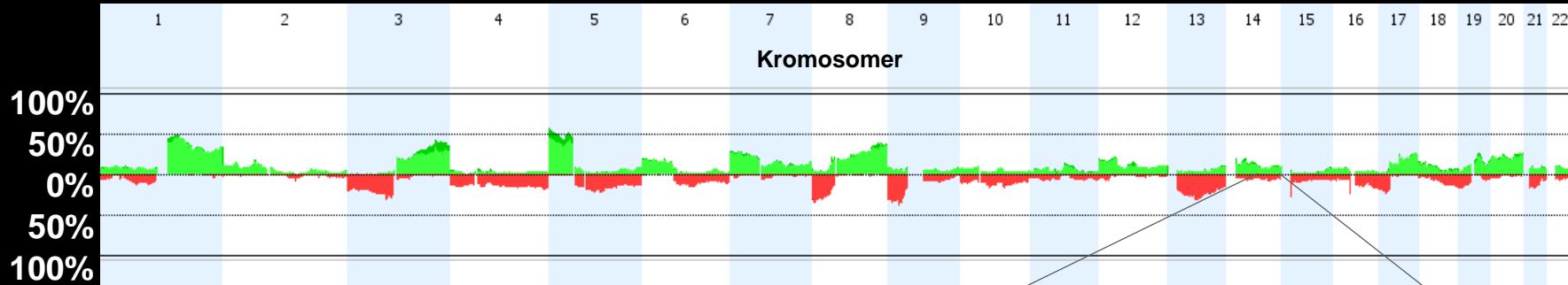
Adenocarcinoma



Sample 14A

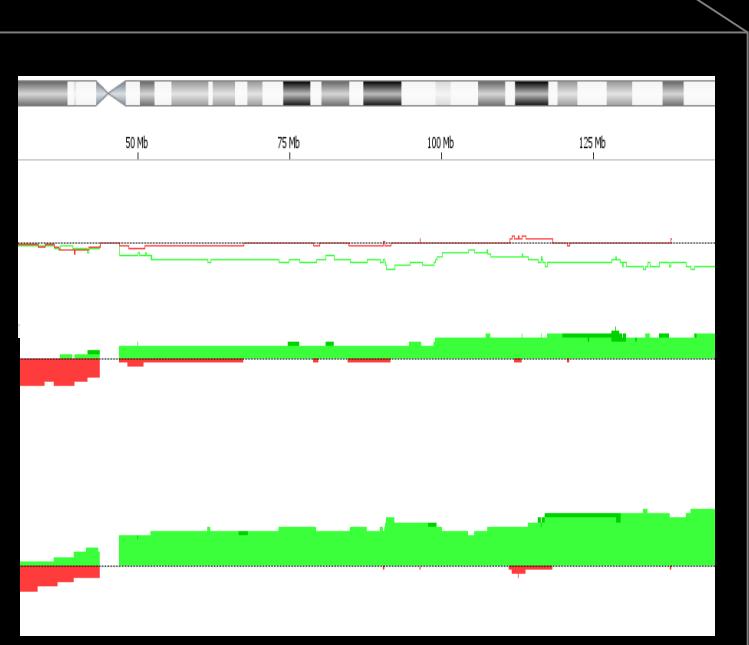
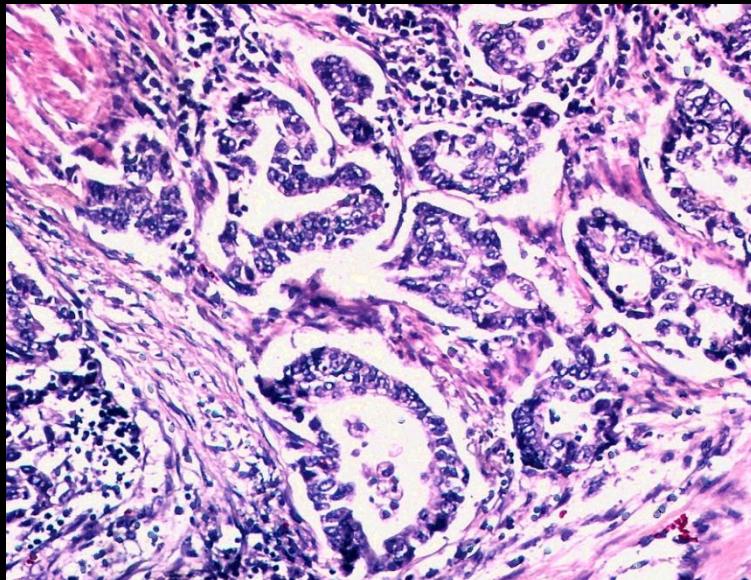
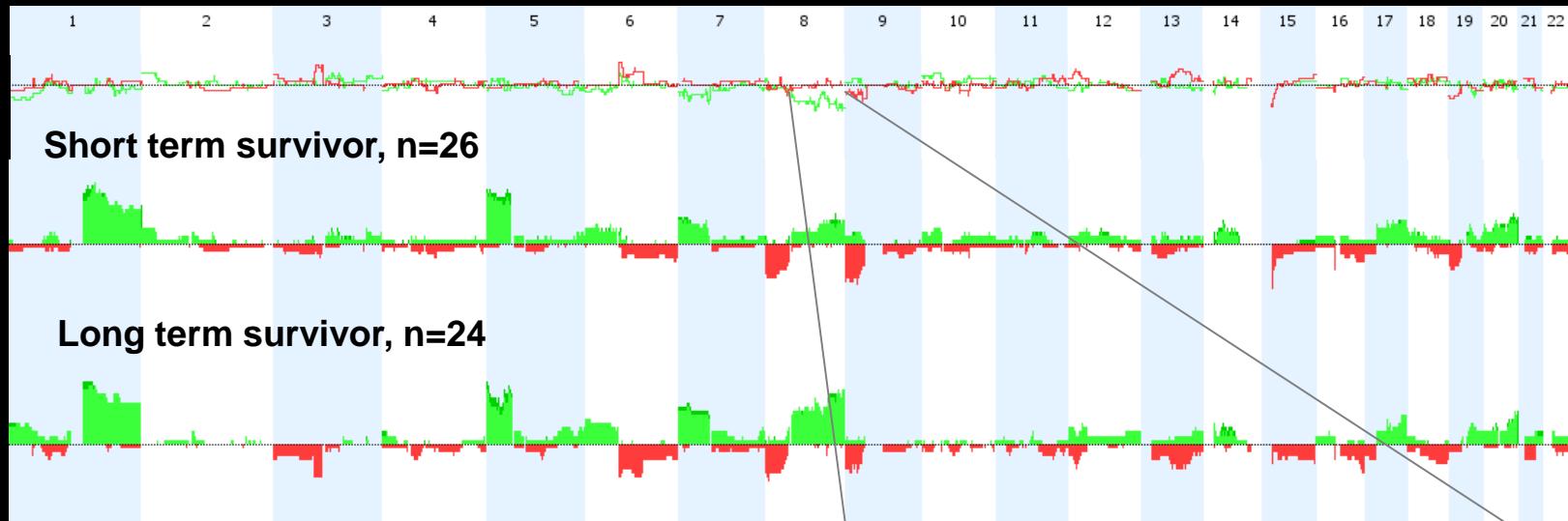


Genetic aberrations define new subgroups of squamous cell carcinoma



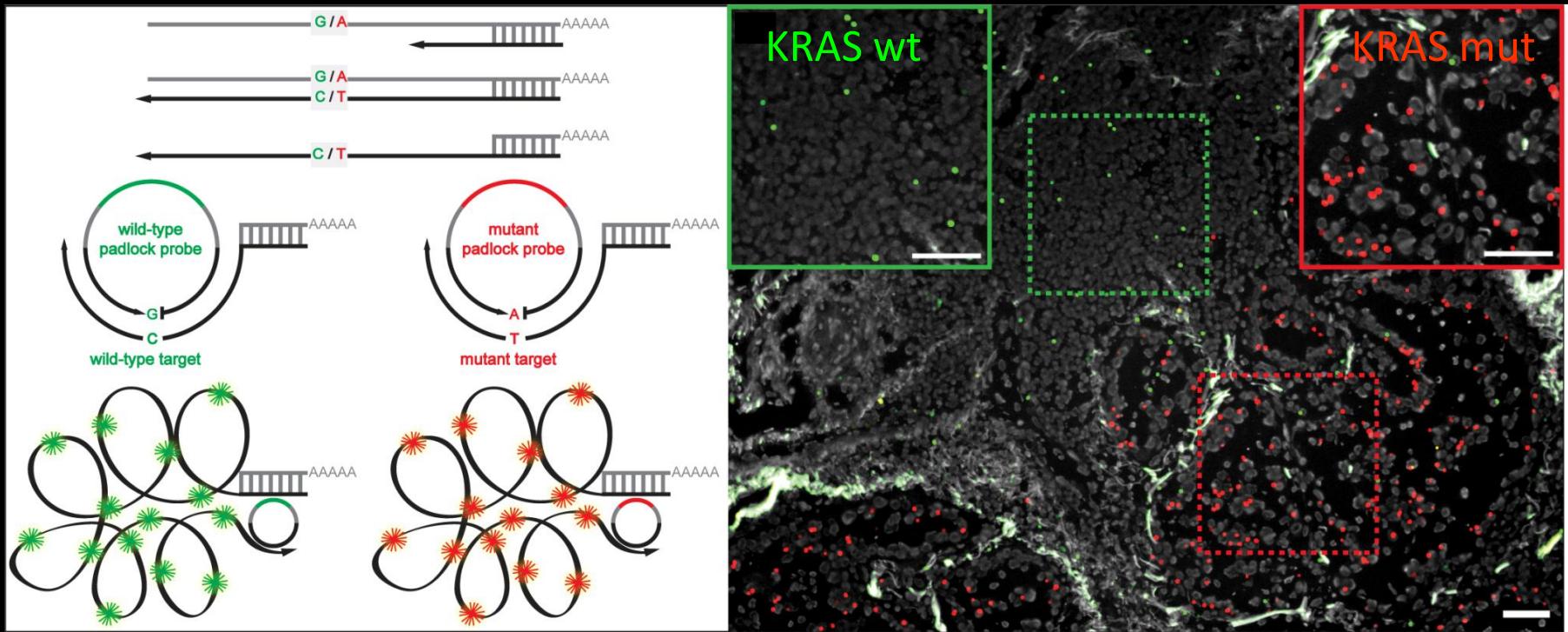
Lars Holmberg
Mats Lambe
Michael Bergqvist
Simon Ekman
Kristina Lamberg
Anders Berglund
Johan Botling
Karolina Edlund
Patrick Micke

Survival region in adenocarcinoma



In situ mutation detection in FFPE tissue

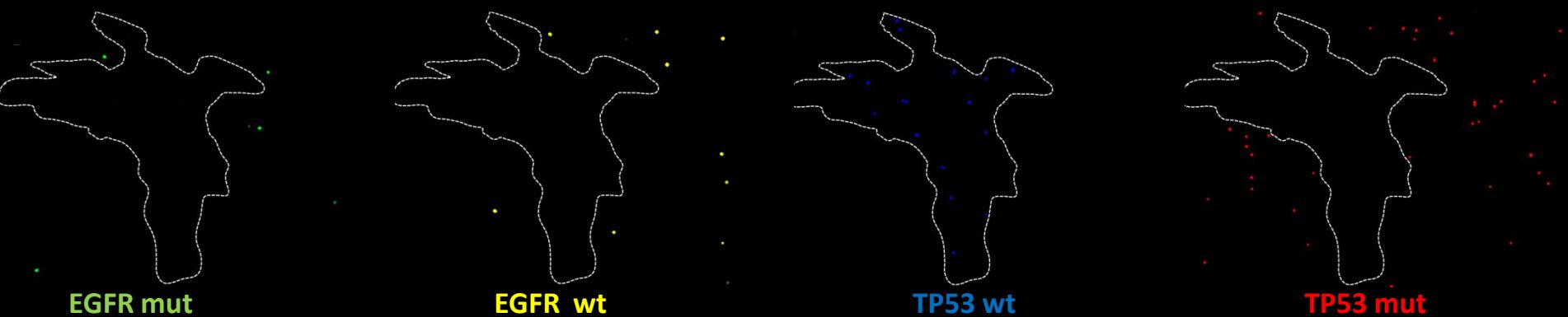
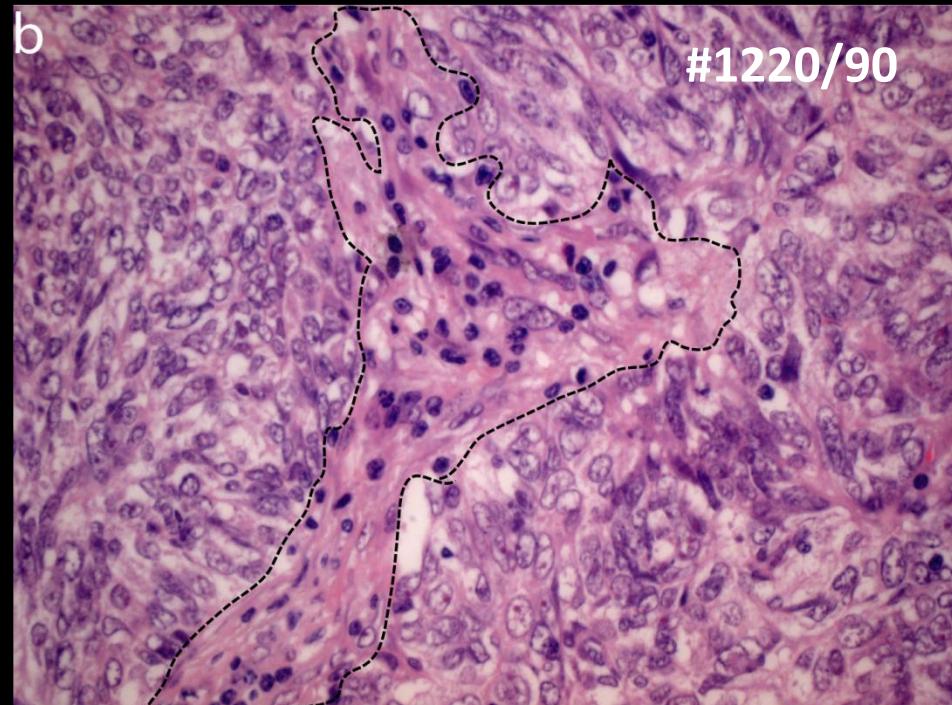
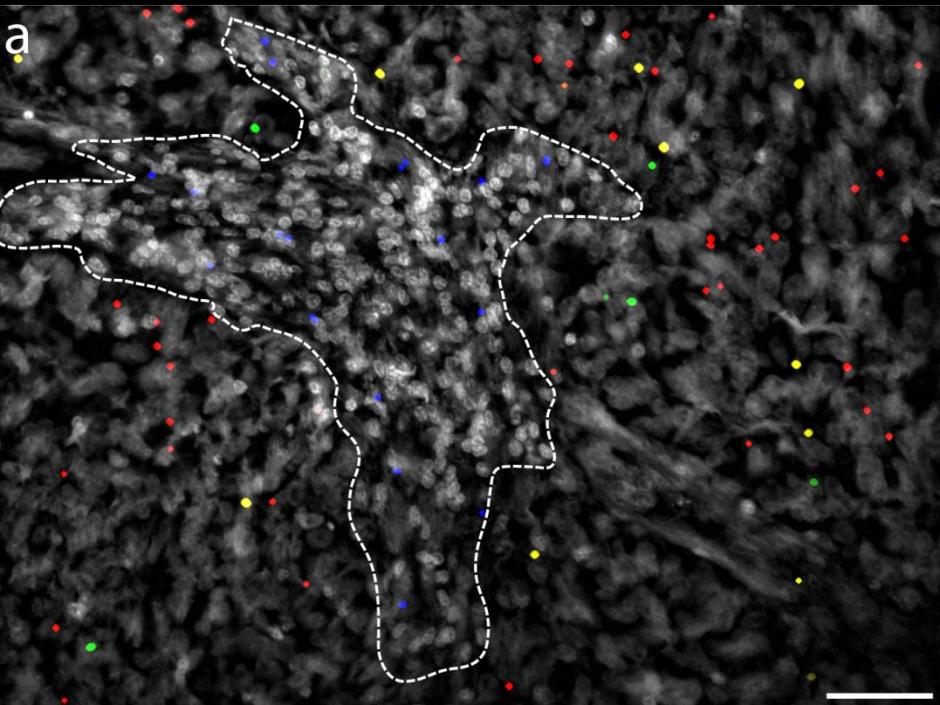
In situ mutation detection of mRNA transcripts by padlock-probes and rolling circle amplification



Johan Botling
Mats Nilsson
Ida Grundberg
Sara Kiflemariam

EGFR/TP53 double mutation detection

EGFR G719A mut TP53 S127F wt
EGFR G719A wt TP53 S127F mut



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- COMDIA consortium - Mats Nilsson, Magnus Sundström
- Regional Oncology Center Uppsala-Örebro - Mats Lambe, Lars Holmberg
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- Universität Dortmund – Jan Hengstler, Jörg Rahnenführer
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- Qiagen



Karolina Edlund



Jan Hengstler



Jörg Rahnenführer

