elcc European Lung Cancer Conference

Poster Discussion 1

74 PD

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3 PD

4 PD

Lukas Bubendorf
Pathology

Universitätsspital Basel

Disclosure

Receipt of grants: *Roche*

Receipt of honoraria / consultation fees: *Roche, Pfizer, Abbott, Boehringer Ingelheim*

Stock shareholder: *Roche, Novartis*

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When is a pathological diagnosis preferred before stereotactic ablative radiotherapy for stage I lung cancer? A decision analysis

Alexander V. Louie, MD, FRCPC

European Lung Cancer Conference

March 2014

Western University · Canada

HARVARD SCHOOL OF PUBLIC HEALTH

London Health Sciences Centre
London Regional Cancer Program

Background

- Stereotactic ablative radiotherapy (SABR) for a suspicious SPN without pathology is acceptable in unfit patients after review in multidisciplinary tumor board

- Appropriate lung cancer prevalence / probability threshold justifying this strategy?
  → Decision analysis

Methods

Three strategies

1. Observation
2. SABR without pathologic confirmation
3. Transthoracic BX prior to SABR

…at different lung cancer prevalences

- Diagnostic test performance: literature
- Toxicity & recurrence data: database of 382 pts treated with SABR

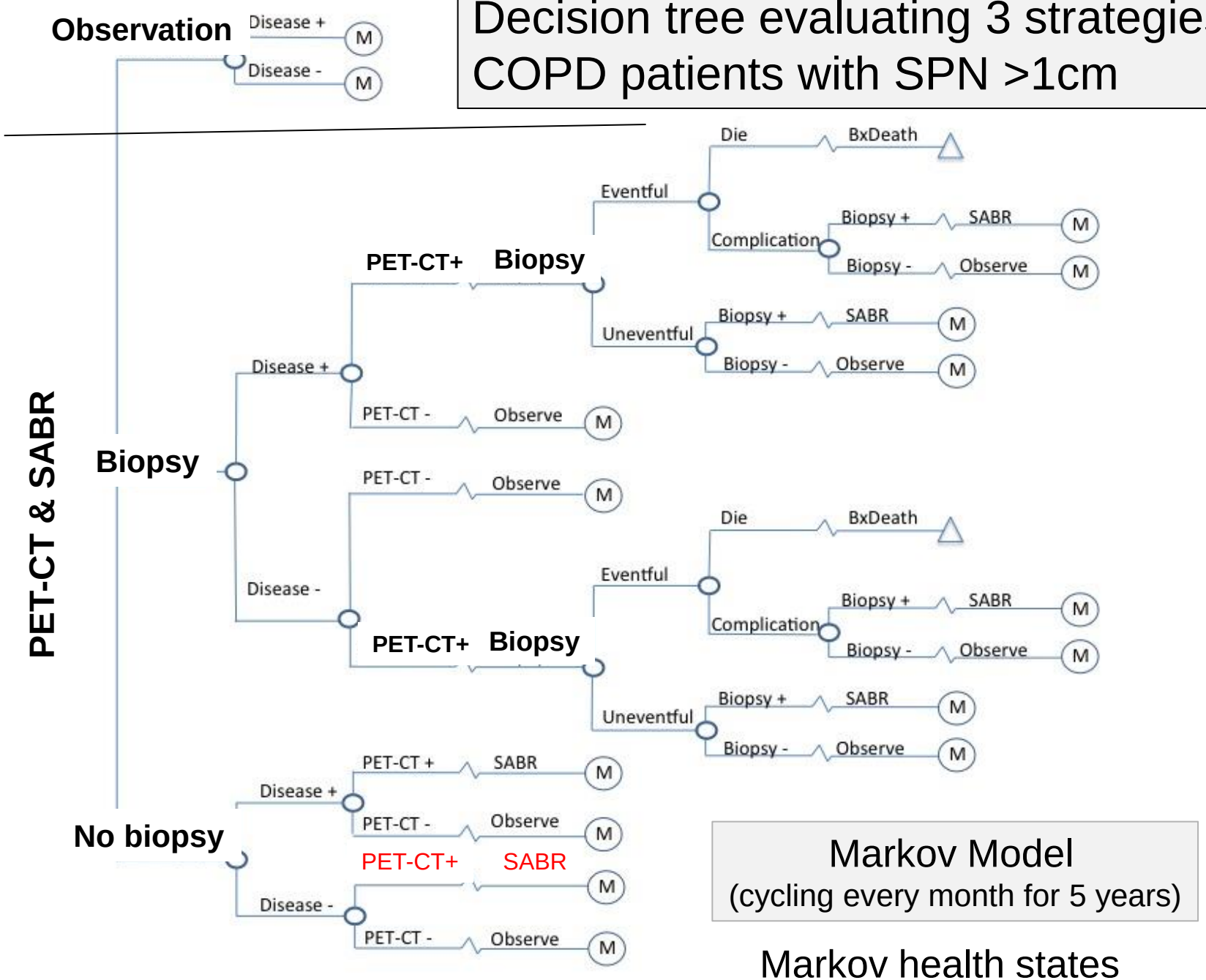
→ Decision tree & Markov model

→ Predict prevalence thresholds

→ Quality adjusted life years (QALYs)

MODEL PARAMETERS	SOURCE
PET-CT sensitivity and specificity	ACCPGuidelines, Gould, *Chest* 2013
Biopsy sensitivity and specificity	Meta-analysis, Cronin, *adiology* 2008
Biopsy-related toxicity	Wiener, *Annals of Internal Medicine* 2011
Biopsy-related death	Gould, *Annals of Internal Medicine* 2003
Patterns of recurrence following SABR	VUMC database - individual patient data
Death following recurrence	Meta-analysis, Group NM-AC JCO 2010
Death from other causes	US standard life tables 2008, www.cdc.gov
SABR toxicity	VUMC database – individual patient data
Treatment-related death from SABR	Meta-analysis, Grutters, *Radiot Oncol* 2010
LR, RR, DM utilities	Meta-analysis, Sturza, *Med Decis Making* 2010
SABR and biopsy toxicities utilities	Doyle, *Lung Cancer* 2008
Utility after SABR	Mapping of VUMC individual QoL database

Decision tree evaluating 3 strategies COPD patients with SPN >1cm



Markov Model
(cycling every month for 5 years)

Markov health states

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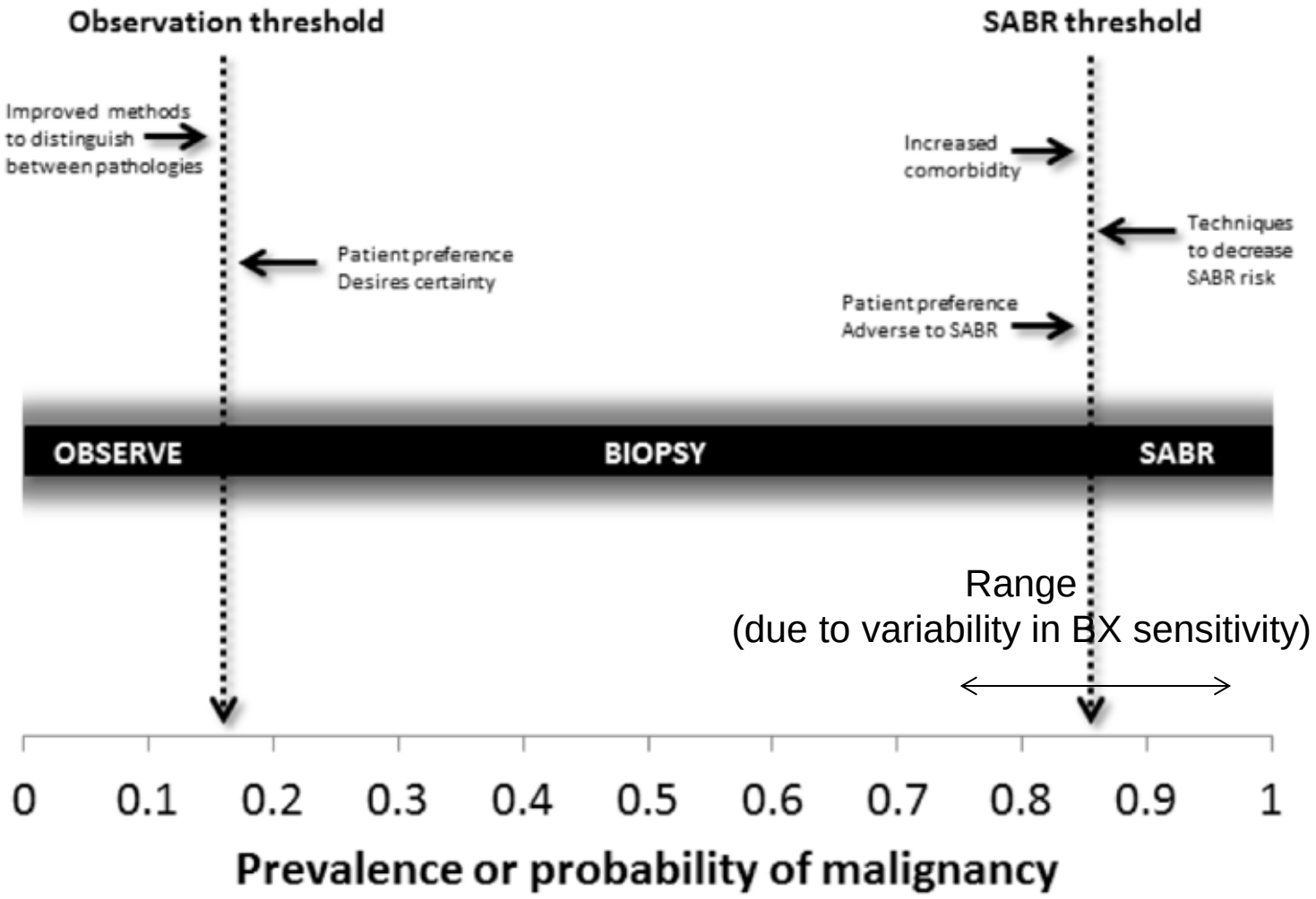
Results



LC prevalence of 65% → QUALYs: 2.09 – 2.64 – 2.56

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Comments

- Help in evidence based decision making in unfit patients
- Complexity by multiple factors → statistical exercise in a dynamic field
- Translating the study results to individual unfit patients with variable degrees of unfitness is difficult

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European Harmonization Study for the immunohistochemical detection of ALK-rearranged NSCLC
(on behalf of all 16 participating institutes enrolled in the study)

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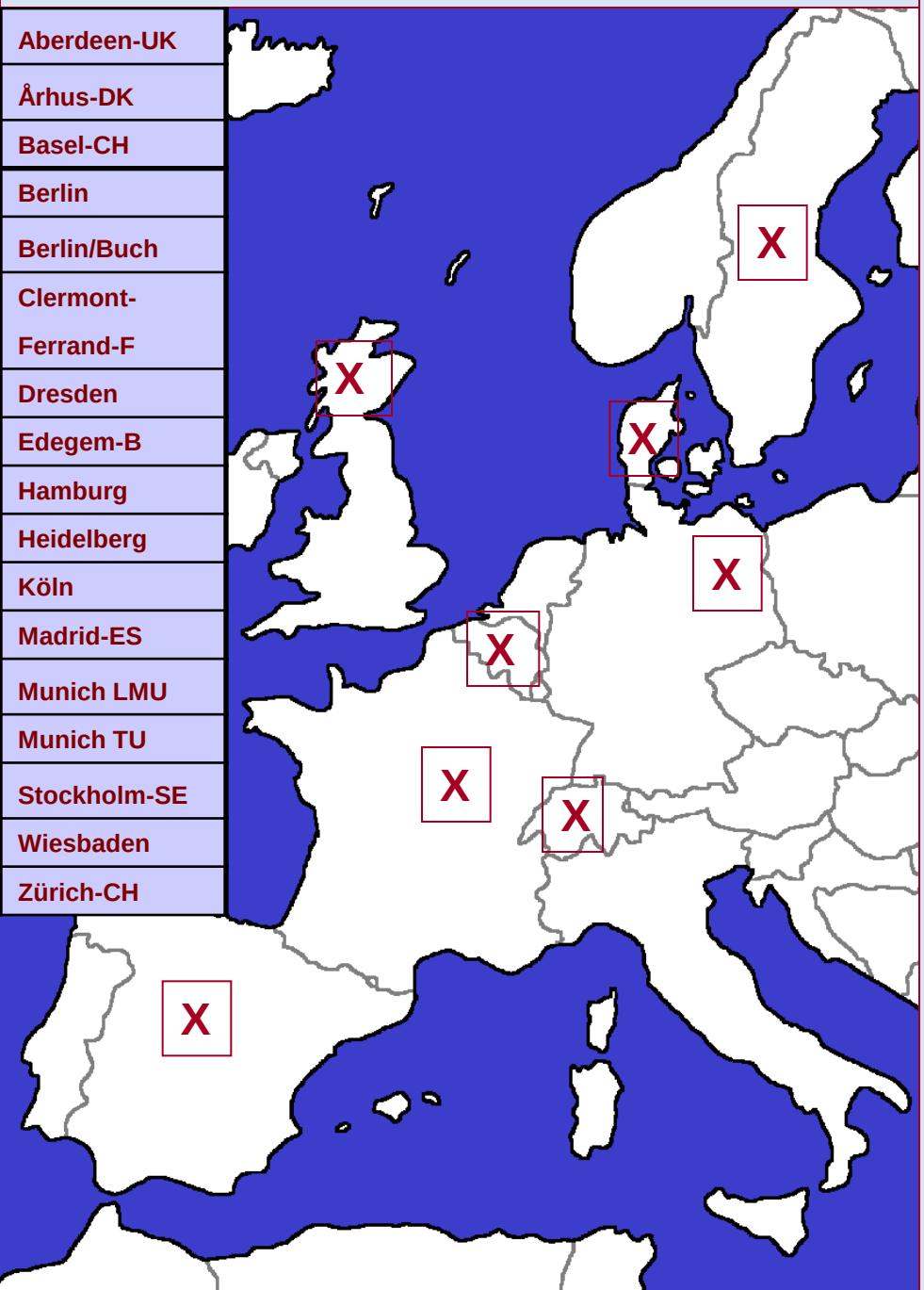
European Harmonization Study for the immunohistochemical detection of ALK-rearranged NSCLC (on behalf of all 16 participating institutes enrolled in the study)

Conflict of interest

(Multi-Centre Immunohistochemical ALK-Testing of Non-Small Cell Lung Cancer Shows High Concordance After Harmonization of Techniques and Interpretation Criteria)

Maximilian von Laffert[1], Arne Warth[2], Roland Penzel[2], Peter Schirmacher[2], Keith M. Kerr[3], Göran Elmberger[4], Hans-Ulrich Schildhaus[5], Reinhard Büttner[5], Fernando Lopez-Rios[6], Simone Reu[7], Thomas Kirchner[7], Patrick Pauwels[8], Katja Specht[9], Enken Drecoll[9], Heinz Höfler[9], Daniela Aust[10], Gustavo Baretton[10], Lukas Bubendorf[11], Sonja Stallmann[12], Annette Fisseler-Eckhoff[12], Alex Soltermann[13], Verena Tischler[13], Holger Moch[13], Frederique Penault-Llorca[14], Hendrik Hager[15], Frank Schäper[16], Dido Lenze[1], Michael Hummel[1] and Manfred Dietel[1]

„ALK-Harmonization-study“



- **16 Institutes, 8 countries**
- **Harmonization:** webinar
  instruments, observer training
- **TMA-based ALK-testing**
- **IHC only (Ventana ALK-D5F3 Optiview)**
- **binary interpretation (pos. vs. neg.)**
- **15 samples (FISH, PCR validated):**
- **7 unequivocally ALK-FISH-neg.**
- **6 unequivocally ALK-FISH-pos.**
- **2 „borderline“ samples („BL“)**
  (RT-PCR:EML4-variants 1 and 3a/b)!!!

Supported by Ventana / Roche

ALK IHC in 8 ALK positive NSCLC

Participant	case 1	case 3	case 6 (BL**)	case 8	case 10 (BL**)	case 11	case 14	case 15
Berlin/Charité, Germany								
Wiesbaden, Germany				FISH		FISH		
Köln, Germany								
Basel, Switzerland								
Aberdeen, United Kindom						FISH*		
Stockholm, Sweden						FISH/PCR		
Madrid, Spain								
Clermont-Ferrand, France				FISH*				
Dresden, Germany						FISH*		
Munich LMU, Germany								
Munich TU, Germany								
Zurich, Switzerland						FISH*		
Edegem, Belgium								
Århus, Denmark								
Berlin/Buch, Germany						FISH*		
Heidelberg, Germany						FISH		

negative positive

All 7 ALK-FISH-negative cases homogenously scored negative by IHC

82 PD Comments

- Ventana ALK Assay: well standardized & robust (harmonization of technique & scoring)
- Not addressed:
  - Pre-analytical variability
  - Other platforms & antibodies (Leica, DAKO)
- Difficult cases exist
- IHC & FISH (ideal world)
- Unequivocal ALK IHC could replace FISH

3PD

ALK and MET are Synergistic Co-Activators of Downstream Signals by Amplification in Pulmonary Sarcomatoid Carcinoma: A Potential Target for Therapy?

Patrizia Gasparini, Gabriella Sozzi, Valentina Ciravolo, Serenella Pupa, Elena Tamborini, Roberto Caserini, Ugo Pastorino, Giuseppe Pelosi

FONDAZIONE IRCCS
ISTITUTO NAZIONALE
DEI TUMORI

Sarcomatoid carcinoma

- Sarcoma-like differentiation (pleomorphic, spindle cell, giant cell, carcinosarcoma, blastoma)
- Characterized by EMT
- Poor prognosis
- Predictive alterations anecdotal
- Targeting EMT as a therapeutic option?

- ALK not re-arranged but “amplified” in 20%
- Scant data on MET

- Prevalence of ALK and MET alterations?
- Functional relationship between ALK & MET?
- Therapeutic targes in PSC

86 PSC

76 PLC, 4 PB, 3 GCC, 2 CS, 1 SpCC
23 stage I, 39 stage II and 24 stage III-IV
5 different Centers

FFPE tissues: all 86 PSC

FISH: ALK and MET gene status:

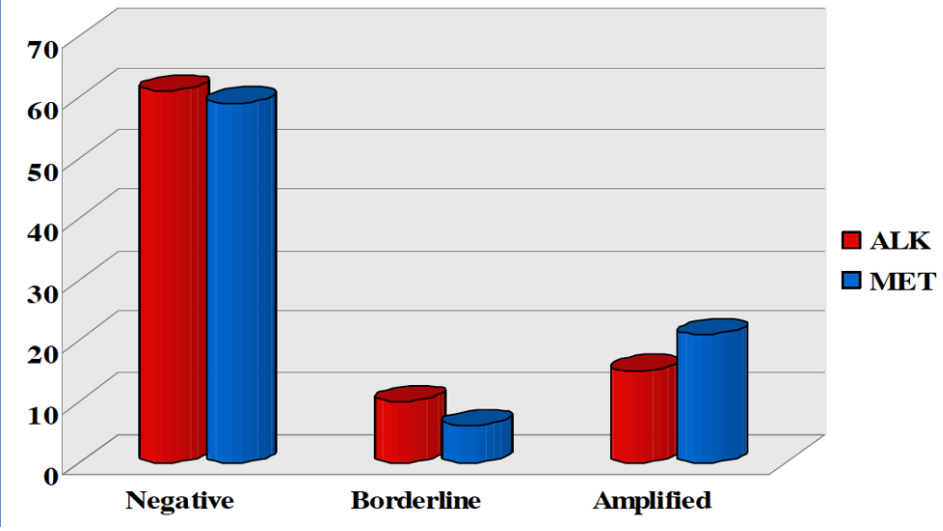
IHC:
ALK and MET protein
Real Time PCR:
mRNA quantification

Frozen tissue: only 8 PSC

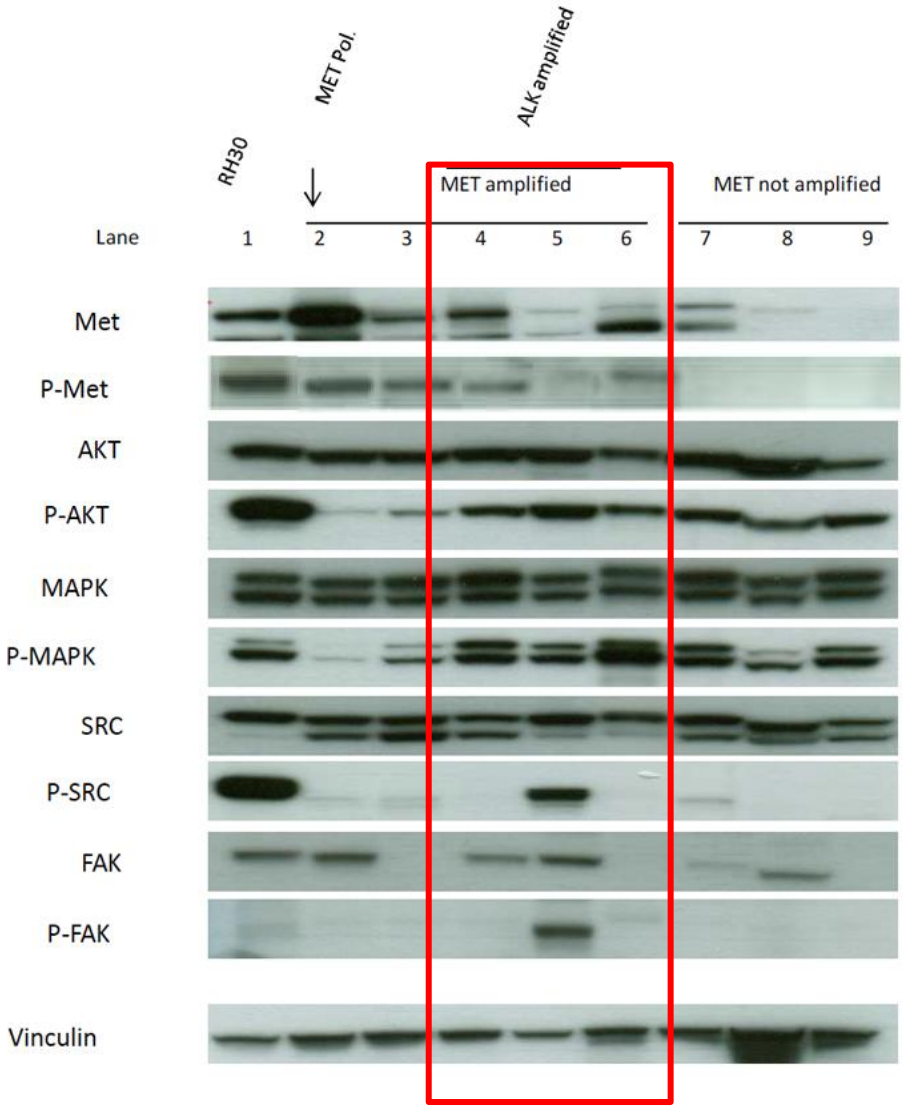
Western Blot :
MET, FAK, SRC, MAPK and AKT and their activated forms

+ biochemical analyses

3PD Results

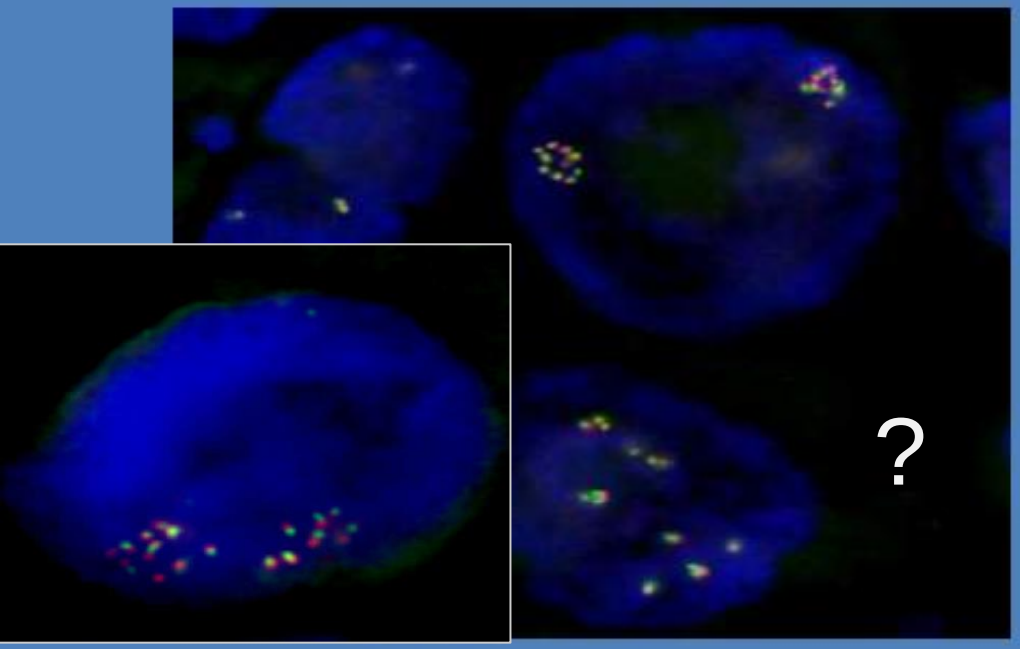


- 18% co-amplification
- Co-amplification α with downstream signal activation (p-SRC & p-FAK) involved in invasion / EMT



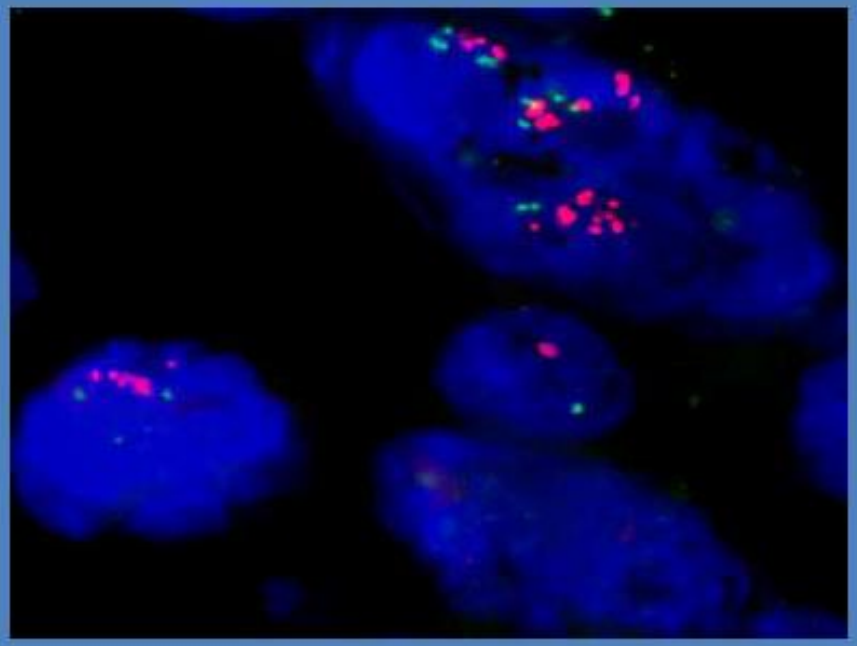
ALK

- No translocation
- 15/86 (17%) amplification
- 10/86 (12%) borderline



MET

- 21/86 (24%) amplification
- 6/86 (7%) borderline



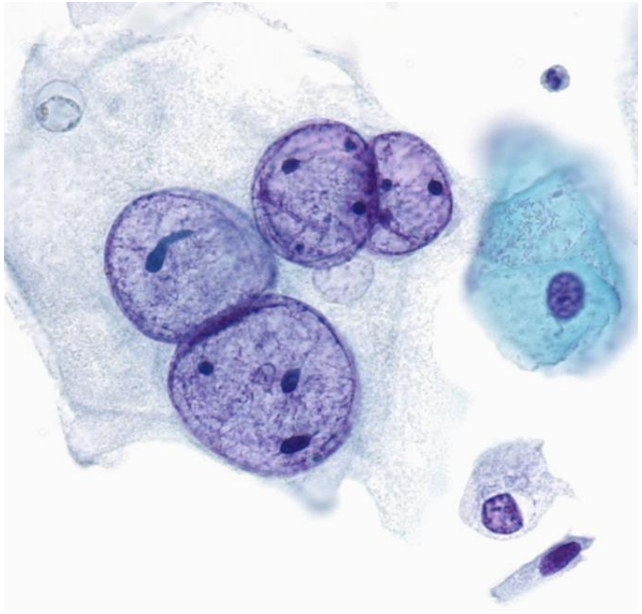
Amplified: ≥ 15 signals of the gene or presence of clusters in >10% of tumor cells.

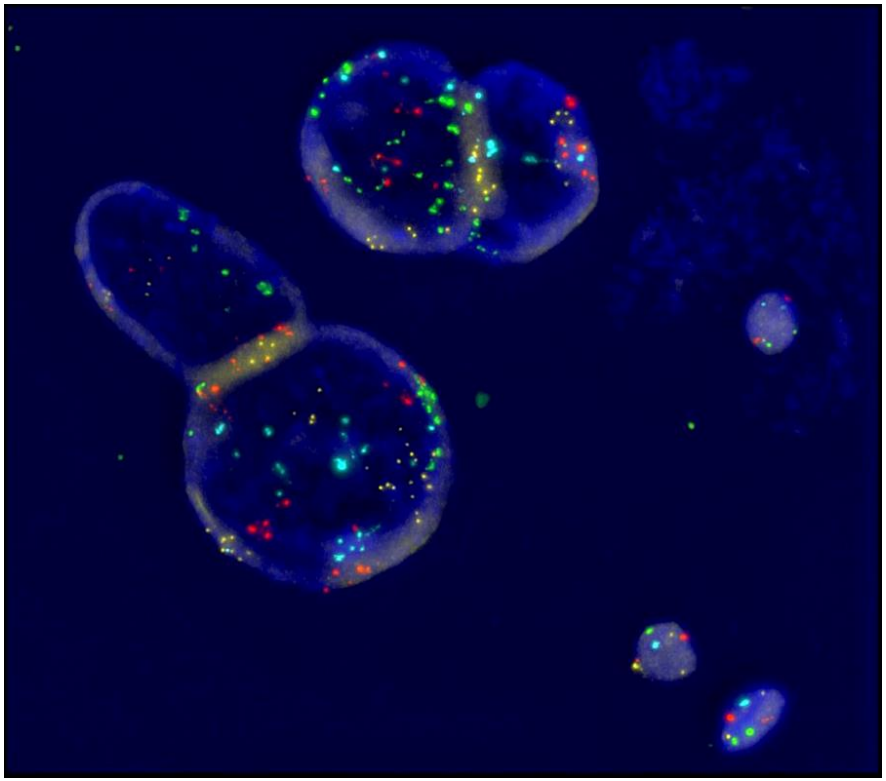
Borderline: ≥ 15 signals of the gene or presence of clusters in 5-10% of tumor cells.

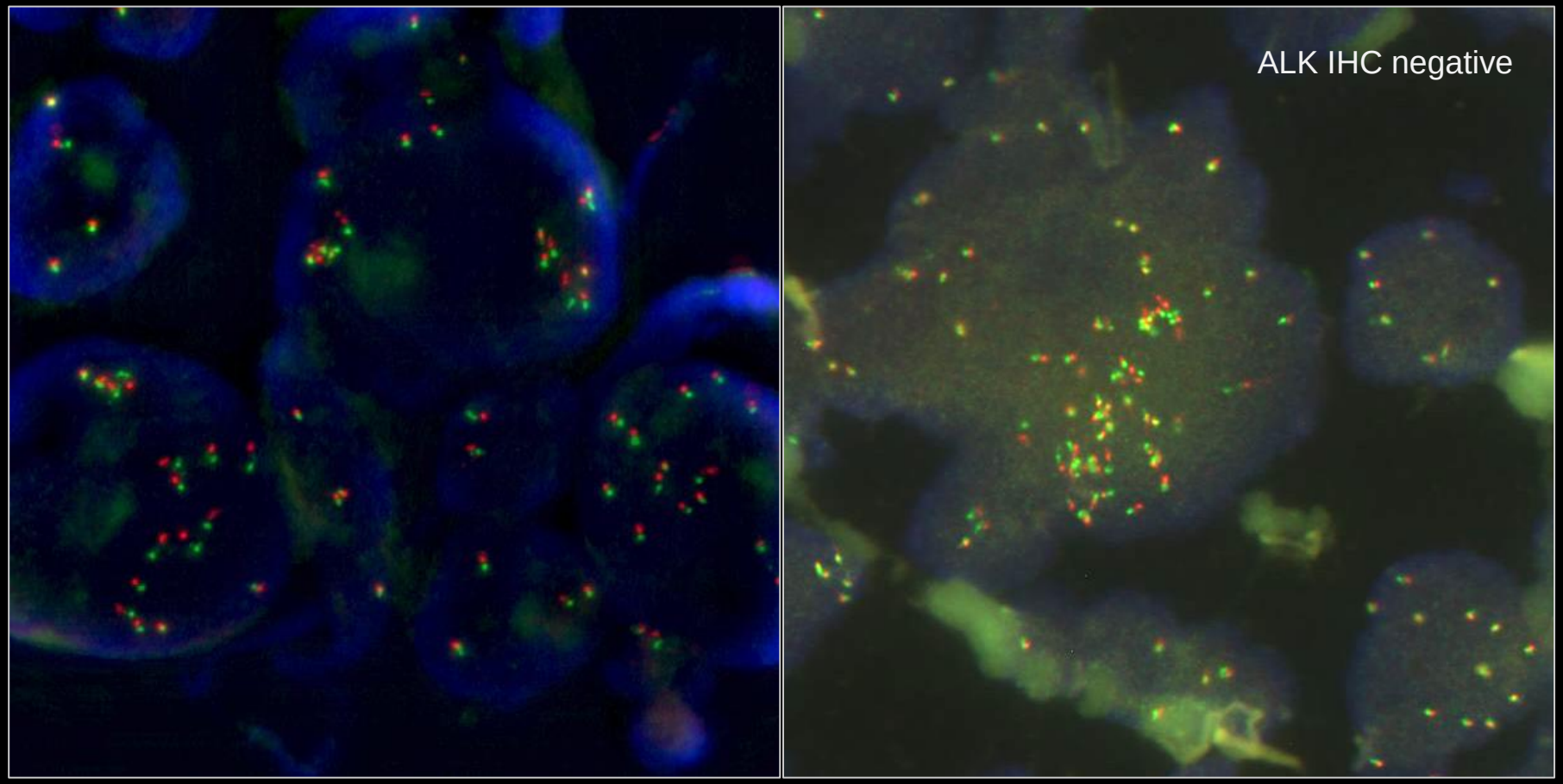
Negative: ≥ 15 signals of the gene or presence of clusters in <5% of tumor cells, or

74 PD "Amplification issue"

- "Amplification" is not well defined
- Polyploidy due to endo-replication is often interpreted as amplification but does not select for specific genes

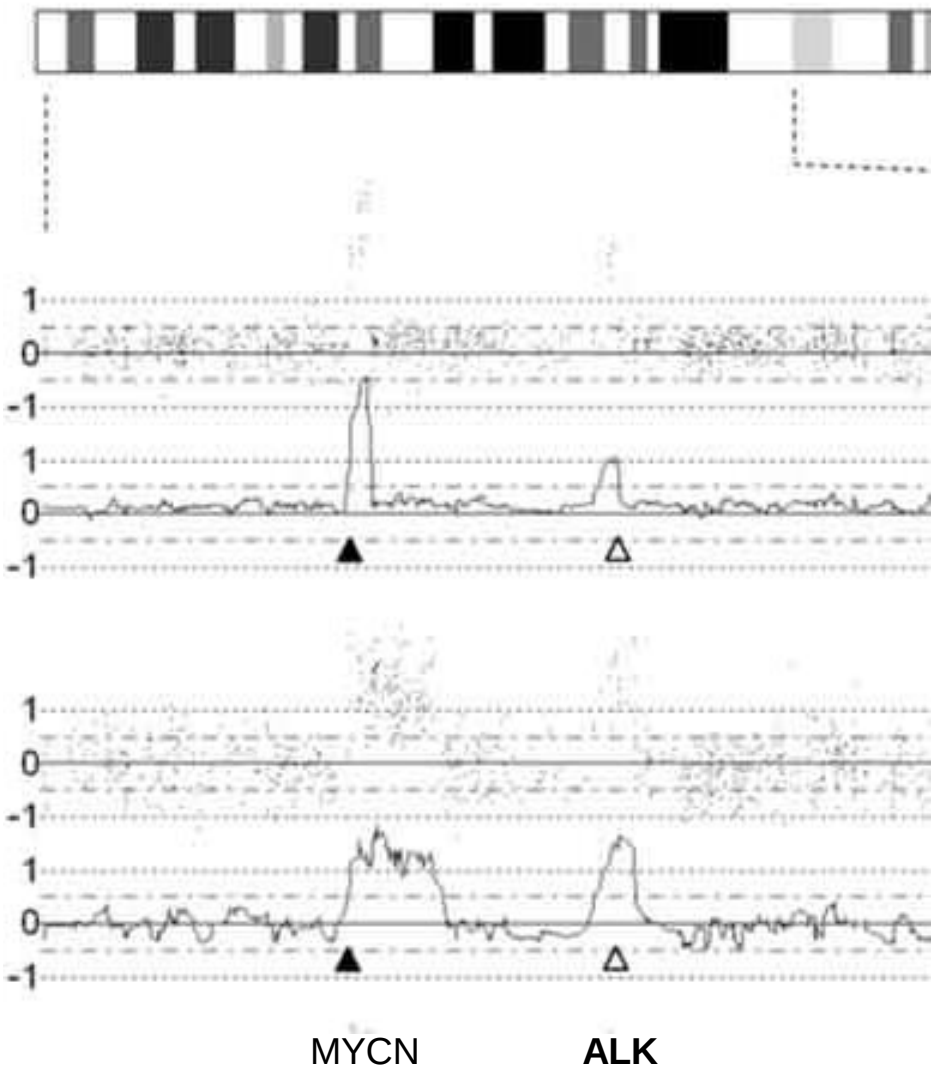






High ALK gene copy number

ALK amplification in Neuroblastoma



Caren H et al, *Biochem J* 2008,416:153

aCGH and NGS data from public databases (NSCLC):

True ALK amplification:
1/>500 NSCLC

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- Interesting hypothesis: synergistic action of ALK and MET in sarcomatoid lung cancer converging to EMT related downstream signaling (p-SRC & p-FAK)
- Limitations:
  - “amplification issue”
  - No statistical analysis (low number of cases)
  - Associations could be circumstantial

4PD

The prognostic effect of IASLC/ATS/ERS classification of lung adenocarcinoma on postrecurrence survival in resected adenocarcinoma

- Jung-Jyh Hung,[1] Teh-Ying Chou,[2] Yu-Chung Wu,[1]
- and Wen-Hu Hsu[1]

[1]Division of Thoracic Surgery, Department of Surgery, Taipei Veterans General Hospital, and School of Medicine, National Yang-Ming University, Taipei, Taiwan
[2]Institute of Clinical Medicine, National Yang-Ming University, and Department of Pathology and Laboratory Medicine, Taipei Veterans General Hospital, Taipei, Taiwan

Objective:

Prognostic factors of PRS in resected lung adenocarcinoma after recurrence.

Methods:

Clinicopathological characteristics of 140 patients

Results:

Independent predictors of worse PRS :

- N2 status (*P* = 0.036),
- Micropapillary/solid predominant pattern (*P* = 0.018)
- No treatment for recurrence (*P* < 0.001)

but not stage (I& II vs. III) and liver metastases

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Comments

- Importance of histological pattern (micropapillary / solid) confirmed
- Limitations:
  - ECOG performance status?
  - Time from resection to recurrence?
  - Number of recurrent organs?
  - EGFR / KRAS status?