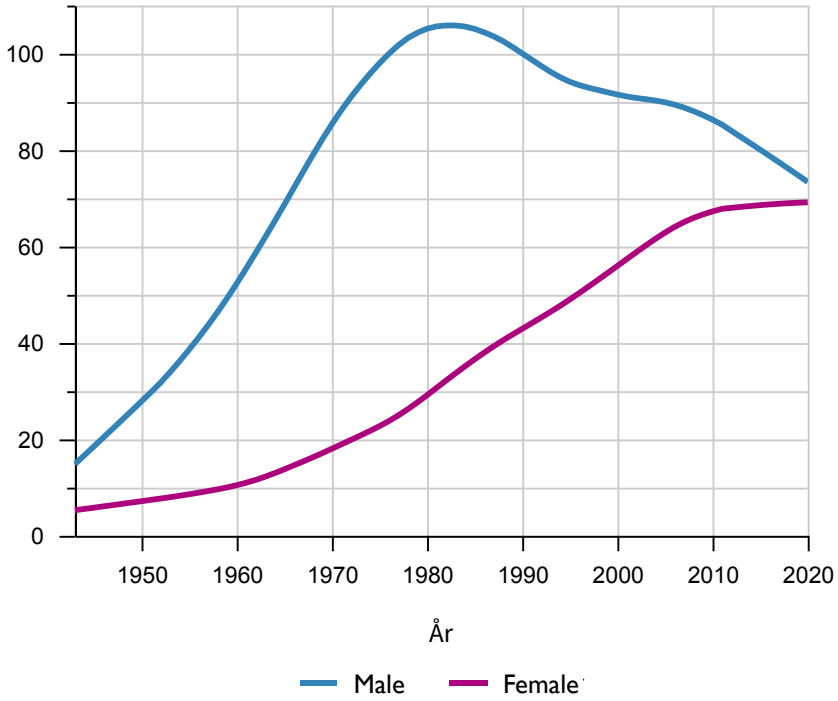
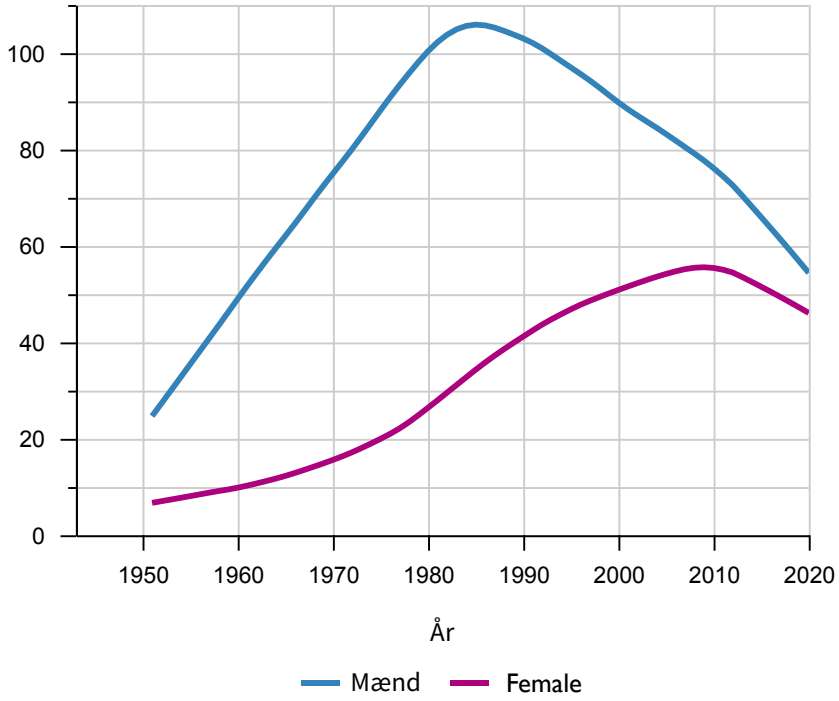
Lung cancer Age's standardized

Incidence new cases/100.000



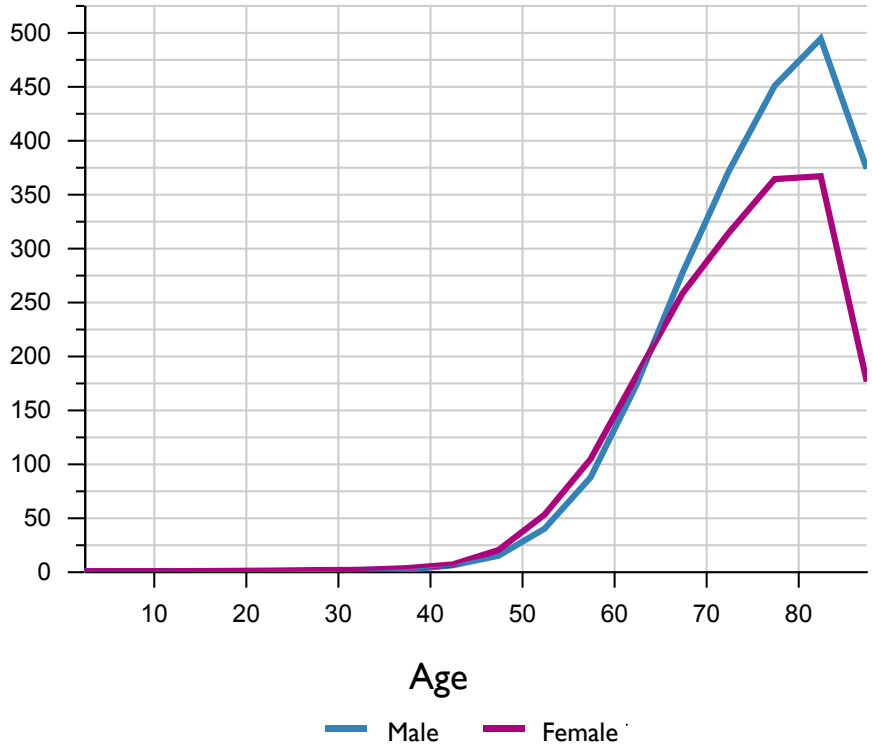
Mortality Death/100.000



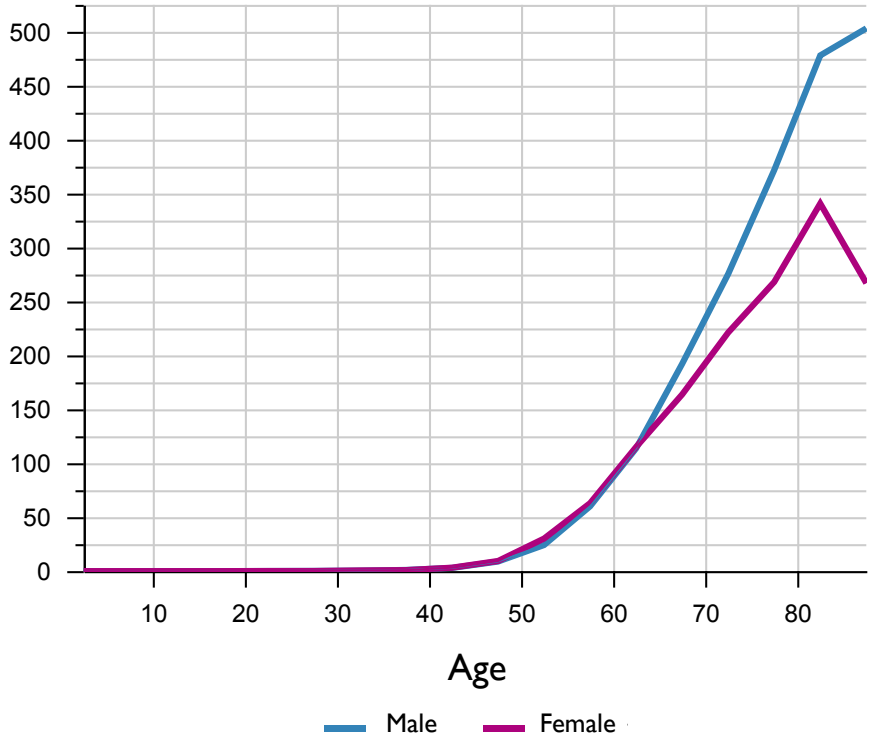
NORDCAN
Association of the Nordic Cancer Registries

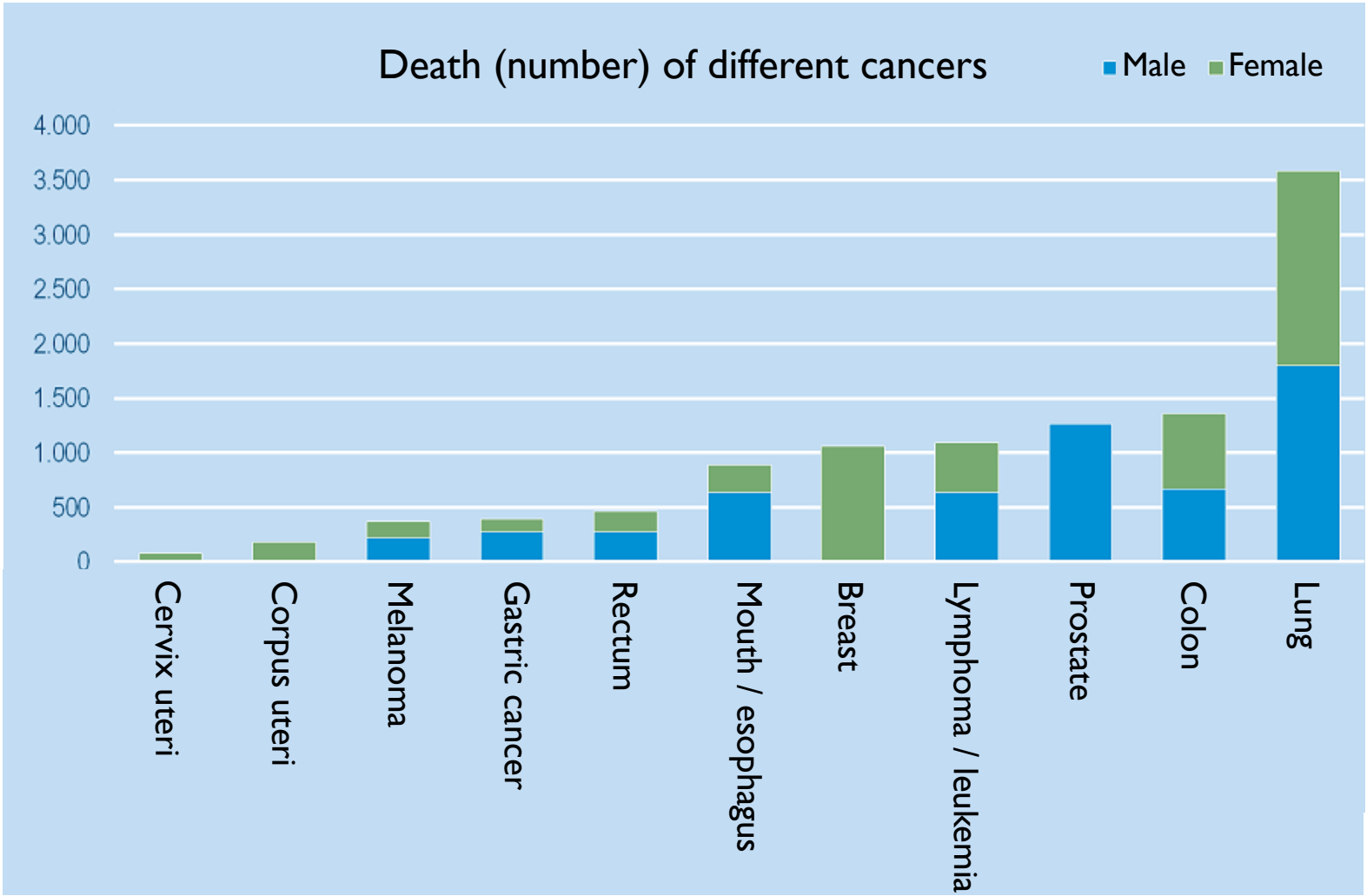
Lung cancer

New cases/100.000 / age interval

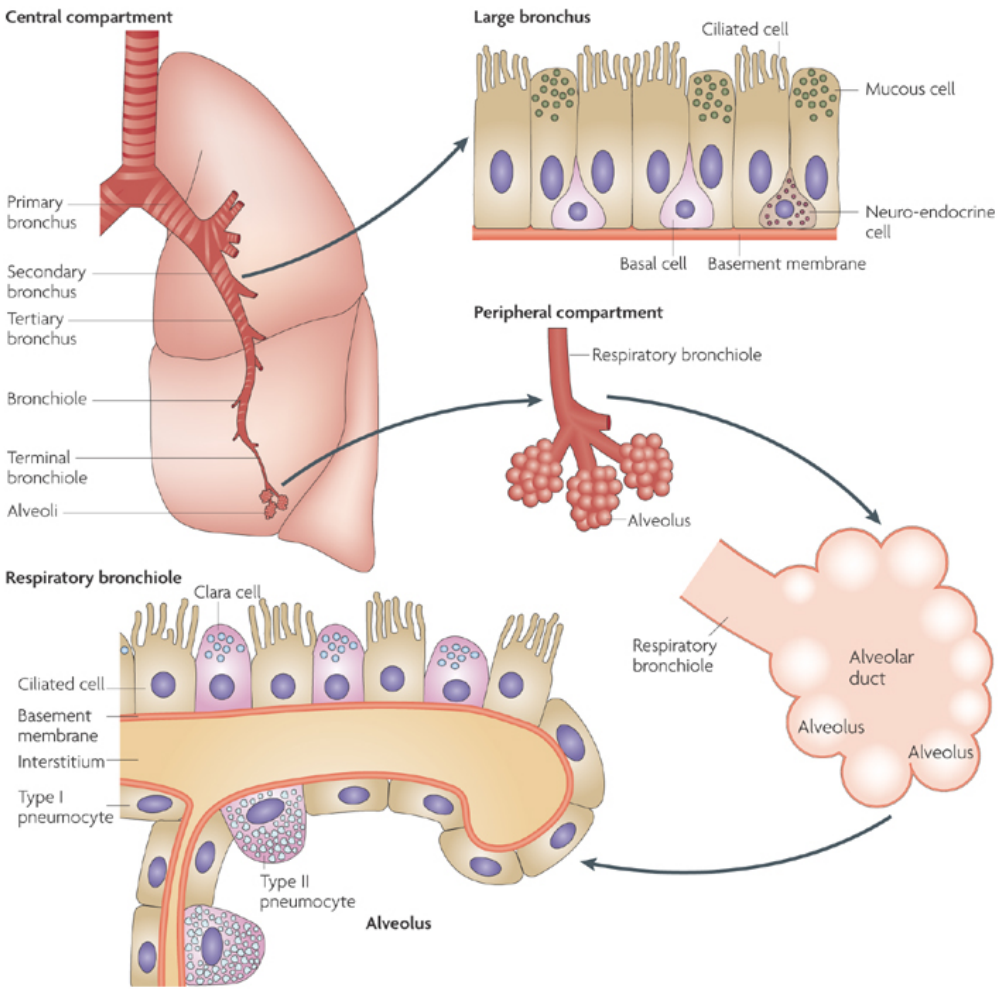


Deaths/100.00 / age interval




Death (number) of different cancers
Male
Female
4.000
3.500
3.000
2.500
2.000
1.500
1.000
500
0
Cervix uteri
Corpus uteri
Melanoma
Gastric cancer
Rectum
Mouth / esophagus
Breast
Lymphoma / leukemia
Prostate
Colon
Lung

Lung Carcinoma



Lung carcinoma derives from stem cells in the lung epithelium

malignant epithelial tumors (carcinomas)

TABLE 1. 2015 WHO Classification of Lung Tumors[a,b,c]

Histologic Type and Subtypes	ICDO Code
Epithelial tumors	
Adenocarcinoma	8140/3
Lepidic adenocarcinoma[e]	8250/3[d]
Acinar adenocarcinoma	8551/3[d]
Papillary adenocarcinoma	8260/3
Micropapillary adenocarcinoma[e]	8265/3
Solid adenocarcinoma	8230/3
Invasive mucinous adenocarcinoma[e]	8253/3[d]
Mixed invasive mucinous and nonmucinous adenocarcinoma	8254/3[d]
Colloid adenocarcinoma	8480/3
Fetal adenocarcinoma	8333/3
Enteric adenocarcinoma[e]	8144/3
Minimally invasive adenocarcinoma[e]	
Nonmucinous	8256/3[d]
Mucinous	8257/3[d]
Preinvasive lesions	
Atypical adenomatous hyperplasia	8250/0[d]
Adenocarcinoma in situ[e]	
Nonmucinous	8250/2[d]
Mucinous	8253/2[d]
Squamous cell carcinoma	8070/3
Keratinizing squamous cell carcinoma[e]	8071/3
Nonkeratinizing squamous cell carcinoma[e]	8072/3
Basaloid squamous cell carcinoma[e]	8083/3
Preinvasive lesion	
Squamous cell carcinoma in situ	8070/2
Neuroendocrine tumors	
Small cell carcinoma	8041/3
Combined small cell carcinoma	8045/3
Large cell neuroendocrine carcinoma	8013/3
Combined large cell neuroendocrine carcinoma	8013/3
Carcinoid tumors	
Typical carcinoid tumor	8240/3
Atypical carcinoid tumor	8249/3
Preinvasive lesion	
Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia	8040/0[d]
Large cell carcinoma	8012/3
Adenosquamous carcinoma	8560/3
Sarcomatoid carcinomas	
Pleomorphic carcinoma	8022/3
Spindle cell carcinoma	8032/3
Giant cell carcinoma	8031/3
Carcinosarcoma	8980/3
Pulmonary blastoma	8972/3
Other and Unclassified carcinomas	
Lymphoepithelioma-like carcinoma	8082/3
NUT carcinoma[e]	8023/3[d]
Salivary gland-type tumors	
Mucoepidermoid carcinoma	8430/3
Adenoid cystic carcinoma	8200/3
Epithelial-myoepithelial carcinoma	8562/3
Pleomorphic adenoma	8940/0

(*Continued*)

TABLE 1. (*Continued*)

Histologic Type and Subtypes	ICDO Code
Papillomas	
Squamous cell papilloma	8052/0
Exophytic	8052/0
Inverted	8053/0
Glandular papilloma	8260/0
Mixed squamous and glandular papilloma	8560/0
Adenomas	
Sclerosing pneumocytoma[e]	8832/0
Alveolar adenoma	8251/0
Papillary adenoma	8260/0
Mucinous cystadenoma	8470/0
Mucous gland adenoma	8480/0
Mesenchymal tumors	
Pulmonary hamartoma	8992/0[d]
Chondroma	9220/0
PEComatous tumors[e]	
Lymphangioleiomyomatosis	9174/1
PEComa, benign[e]	8714/0
Clear cell tumor	8005/0
PEComa, malignant[e]	8714/3
Congenital peribronchial myofibroblastic tumor	8827/1
Diffuse pulmonary lymphangiomatosis	
Inflammatory myofibroblastic tumor	8825/1
Epithelioid hemangioendothelioma	9133/3
Pleuropulmonary blastoma	8973/3
Synovial sarcoma	9040/3
Pulmonary artery intimal sarcoma	9137/3
Pulmonary myxoid sarcoma with *EWSR1–CREB1* translocation[e]	8842/3[d]
Myoepithelial tumors[e]	
Myoepithelioma	8982/0
Myoepithelial carcinoma	8982/3
Lymphohistiocytic tumors	
Extranodal marginal zone lymphomas of mucosa-associated Lymphoid tissue (MALT lymphoma)	9699/3
Diffuse large cell lymphoma	9680/3
Lymphomatoid granulomatosis	9766/1
Intravascular large B cell lymphoma[e]	9712/3
Pulmonary Langerhans cell histiocytosis	9751/1
Erdheim–Chester disease	9750/1
Tumors of ectopic origin	
Germ cell tumors	
Teratoma, mature	9080/0
Teratoma, immature	9080/1
Intrapulmonary thymoma	8580/3
Melanoma	8270/3
Meningioma, NOS	9530/0
Metastatic tumors	

[a]The morphology codes are from the ICDO.[2] Behavior is coded /0 for benign tumors, /1 for unspecified, borderline or uncertain behavior, /2 for carcinoma in situ and grade III intraepithelial neoplasia, and /3 for malignant tumors.

[b]The classification is modified from the previous WHO classification[3] taking into account changes in our understanding of these lesions.

[c]This table is reproduced from the 2015 WHO Classification by Travis et al.[1]

[d]These new codes were approved by the International Agency on Cancer Research/WHO Committee for ICDO.

[e]New terms changed or entities added since 2004 WHO Classification.[3]

LCNEC, large cell neuroendocrine carcinoma, WHO, World Health Organization; ICDO International Classification of Diseases for Oncology.

Adenocarcinoma (45%)
Squamous carcinoma (18%)
Large cell neuroendocrine carcinoma (1%)
Small cell carcinoma (12%)

TABLE 1. 2015 WHO Classification of Lung Tumors[a,b,c]

Histologic Type and Subtypes	ICDO Code
Epithelial tumors	
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Solid adenocarcinoma	8230/3
Invasive mucinous adenocarcinoma[e]	8253/3[d]
Mixed invasive mucinous and nonmucinous adenocarcinoma	8254/3[d]
Colloid adenocarcinoma	8480/3
Fetal adenocarcinoma	8333/3
Enteric adenocarcinoma[e]	8144/3
Minimally invasive adenocarcinoma[e]	
Nonmucinous	8256/3[d]
Mucinous	8257/3[d]
Preinvasive lesions	
Atypical adenomatous hyperplasia	8250/0[d]
Adenocarcinoma in situ[e]	
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Squamous cell carcinoma	8070/3
Keratinizing squamous cell carcinoma[e]	8071/3
Nonkeratinizing squamous cell carcinoma[e]	8072/3
Basaloid squamous cell carcinoma[e]	8083/3
Preinvasive lesion	
Squamous cell carcinoma in situ	8070/2
Neuroendocrine tumors	
Small cell carcinoma	8041/3
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Carcinoid tumors	
Typical carcinoid tumor	8240/3
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Preinvasive lesion	
Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia	8040/0[d]
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Adenosquamous carcinoma	8560/3
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Giant cell carcinoma	8031/3
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Other and Unclassified carcinomas	
Lymphoepithelioma-like carcinoma	8082/3
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Salivary gland-type tumors	
Mucoepidermoid carcinoma	8430/3
Adenoid cystic carcinoma	8200/3
Epithelial-myoepithelial carcinoma	8562/3
Pleomorphic adenoma	8940/0

(*Continued*)

TABLE 1. (*Continued*)

Histologic Type and Subtypes	ICDO Code
Papillomas	
Squamous cell papilloma	8052/0
Exophytic	8052/0
Inverted	8053/0
Glandular papilloma	8260/0
Mixed squamous and glandular papilloma	8560/0
Adenomas	
Sclerosing pneumocytoma[e]	8832/0
Alveolar adenoma	8251/0
Papillary adenoma	8260/0
Mucinous cystadenoma	8470/0
Mucous gland adenoma	8480/0
Mesenchymal tumors	
Pulmonary hamartoma	8992/0[d]
Chondroma	9220/0
PEComatous tumors[e]	
Lymphangioleiomyomatosis	9174/1
PEComa, benign[e]	8714/0
Clear cell tumor	8005/0
PEComa, malignant[e]	8714/3
Congenital peribronchial myofibroblastic tumor	8827/1
Diffuse pulmonary lymphangiomatosis	
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Epithelioid hemangioendothelioma	9133/3
Pleuropulmonary blastoma	8973/3
Synovial sarcoma	9040/3
Pulmonary artery intimal sarcoma	9137/3
Pulmonary myxoid sarcoma with *EWSR1–CREB1* translocation[e]	8842/3[d]
Myoepithelial tumors[e]	
Myoepithelioma	8982/0
Myoepithelial carcinoma	8982/3
Lymphohistiocytic tumors	
Extranodal marginal zone lymphomas of mucosa-associated Lymphoid tissue (MALT lymphoma)	9699/3
Diffuse large cell lymphoma	9680/3
Lymphomatoid granulomatosis	9766/1
Intravascular large B cell lymphoma[e]	9712/3
Pulmonary Langerhans cell histiocytosis	9751/1
Erdheim–Chester disease	9750/1
Tumors of ectopic origin	
Germ cell tumors	
Teratoma, mature	9080/0
Teratoma, immature	9080/1
Intrapulmonary thymoma	8580/3
Melanoma	8270/3
Meningioma, NOS	9530/0
Metastatic tumors	

[a]The morphology codes are from the ICDO.[2] Behavior is coded /0 for benign tumors, /1 for unspecified, borderline or uncertain behavior, /2 for carcinoma in situ and grade III intraepithelial neoplasia, and /3 for malignant tumors.

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Carcinoids 1 - 2%

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Fetal adenocarcinoma	8333/3
Enteric adenocarcinoma[e]	8144/3
Minimally invasive adenocarcinoma[e]	
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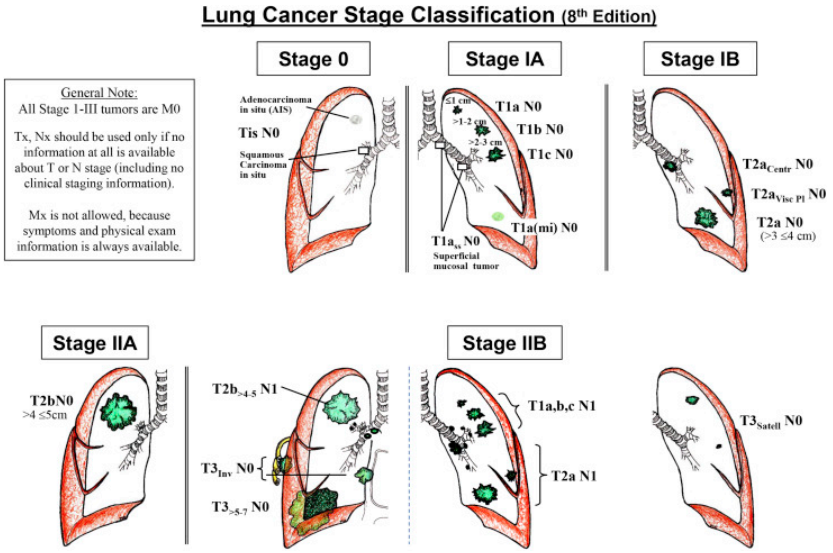
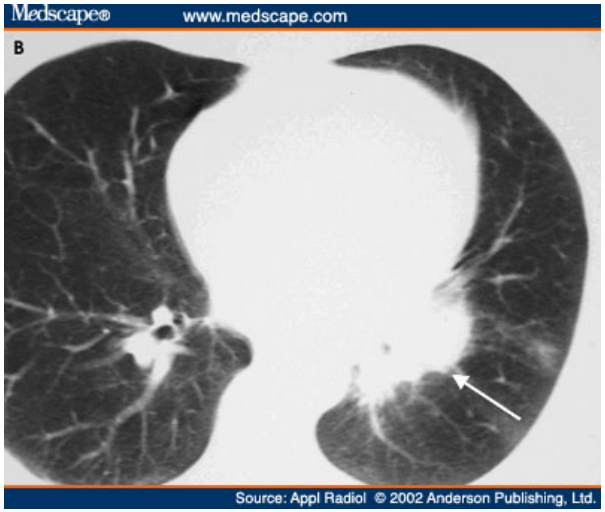
Diagnostic sampling

Adenocarcinoma (45%)
Squamous carcinoma (18%)
Large cell neuroendocrine carcinoma (1%)
Small cell carcinoma (12%)

1. Diagnosis
2. Tumor, Node, Metastasis (TNM)





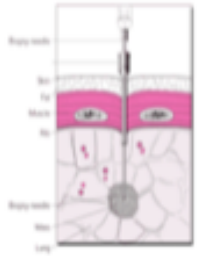
Central tumor

Periferal tumor

Tumor Diagnosis

Bronchial brushing,
Bronchial lavage,
Tissue Biopsi

Fine- or
Course needle
biopsi



Tumor type

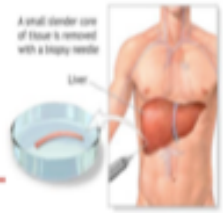
Diagnosis of metastases

EBUS
EUS

N

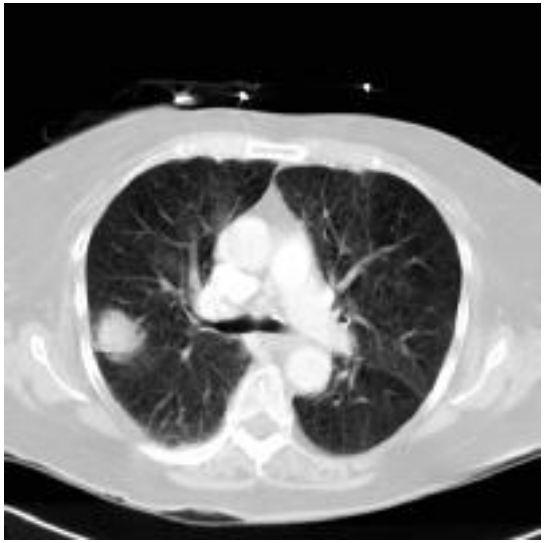
M

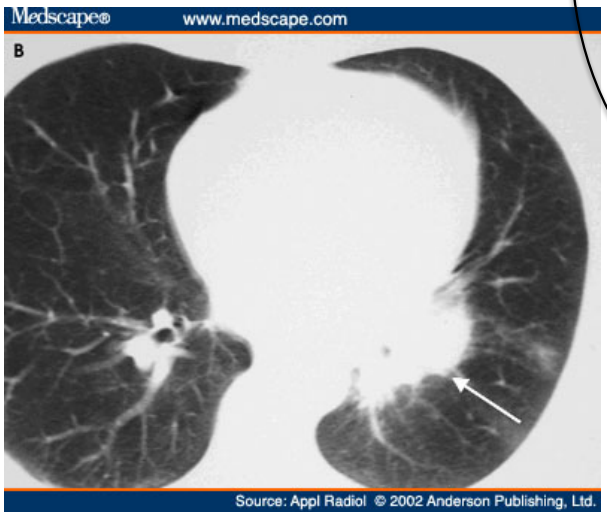
Fine- or courseneedle biopsi
from metastasis suspekte
areas (found by CT eller PET scan)



Not operabel

Operabel

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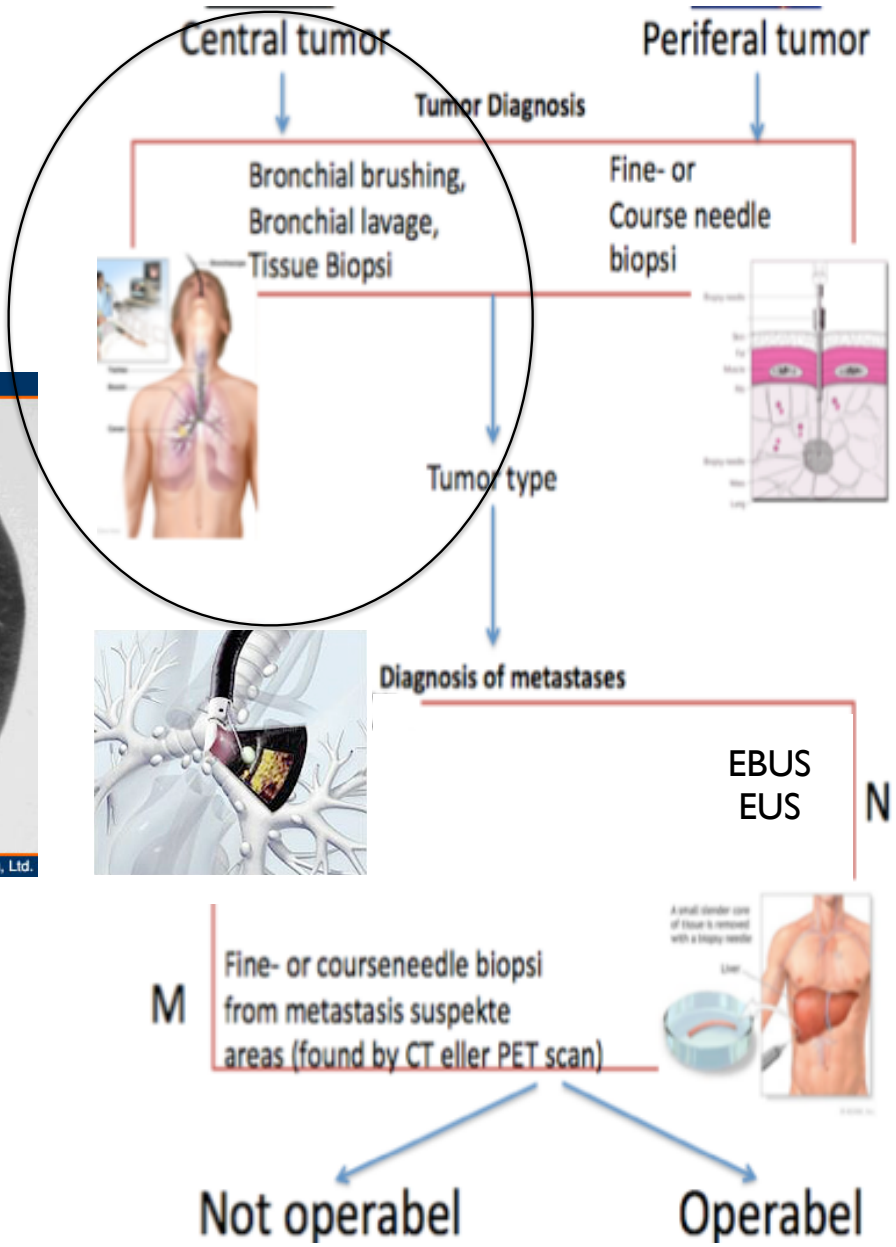
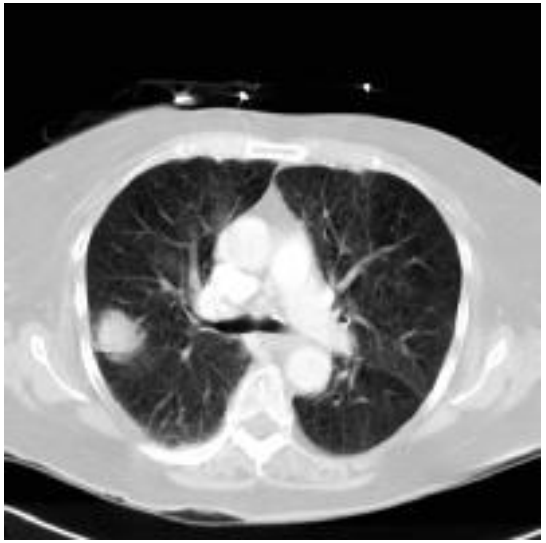
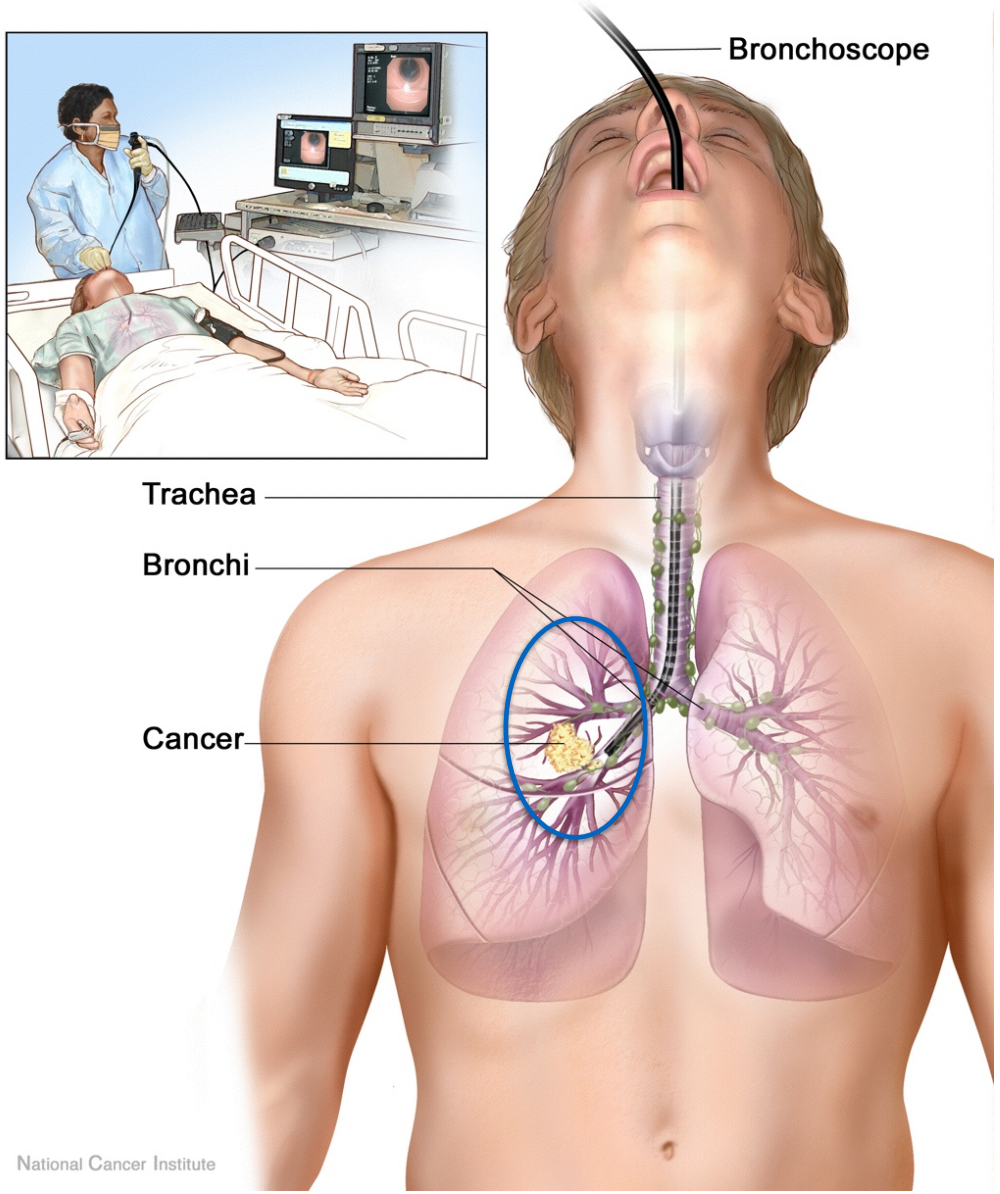

Central tumor
Periferal tumor
Tumor Diagnosis
Bronchial brushing,
Bronchial lavage,
Tissue Biopsi
Fine- or
Course needle
biopsi
Tumor type
Diagnosis of metastases
EBUS
EUS
N
M
Fine- or courseneedle biopsi
from metastasis suspekte
areas (found by CT eller PET scan)
Not operabel
Operabel





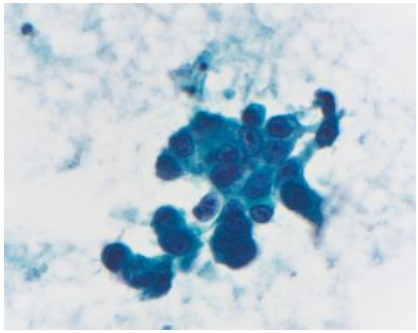
Bronkialwash

Brushbiopsy

EBUS *Endobronchial Ultrasound Scanning*

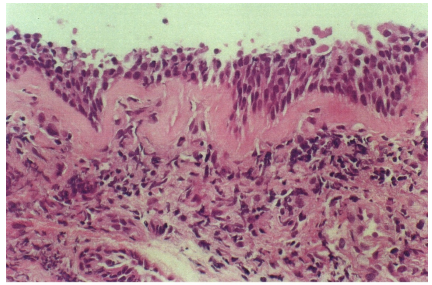
EUS *Esophagal Ultraspund Scanning*

} TBNA

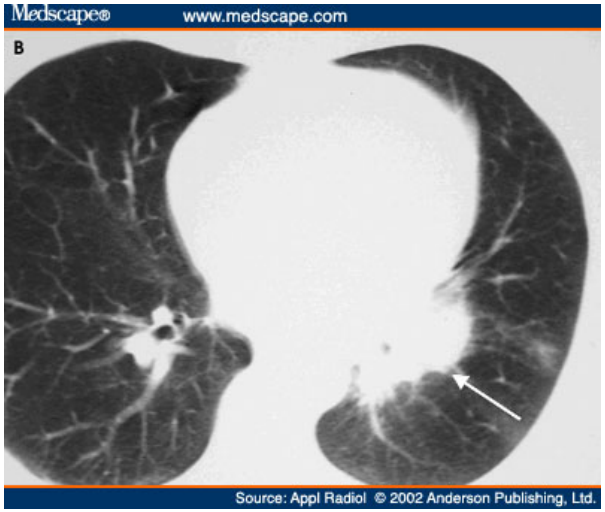


Cytology

forceps biopsy



Histology



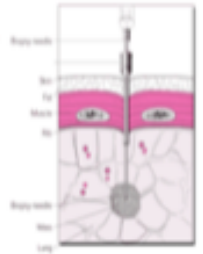
Central tumor

Periferal tumor

Tumor Diagnosis

Bronchial brushing,
Bronchial lavage,
Tissue Biopsi

Fine- or
Course needle
biopsi



Tumor type

Diagnosis of metastases

EBUS
EUS

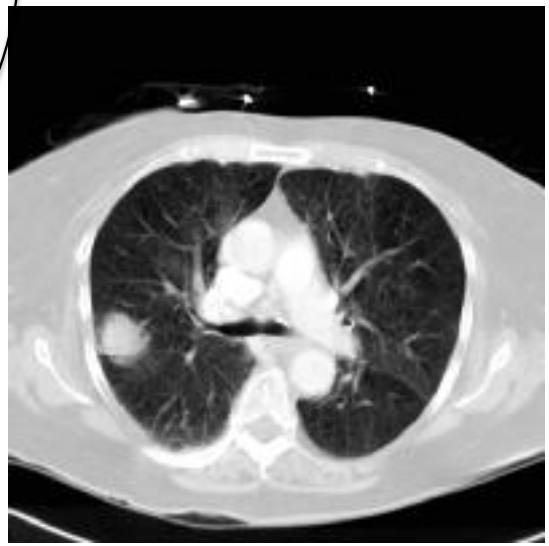
N

M

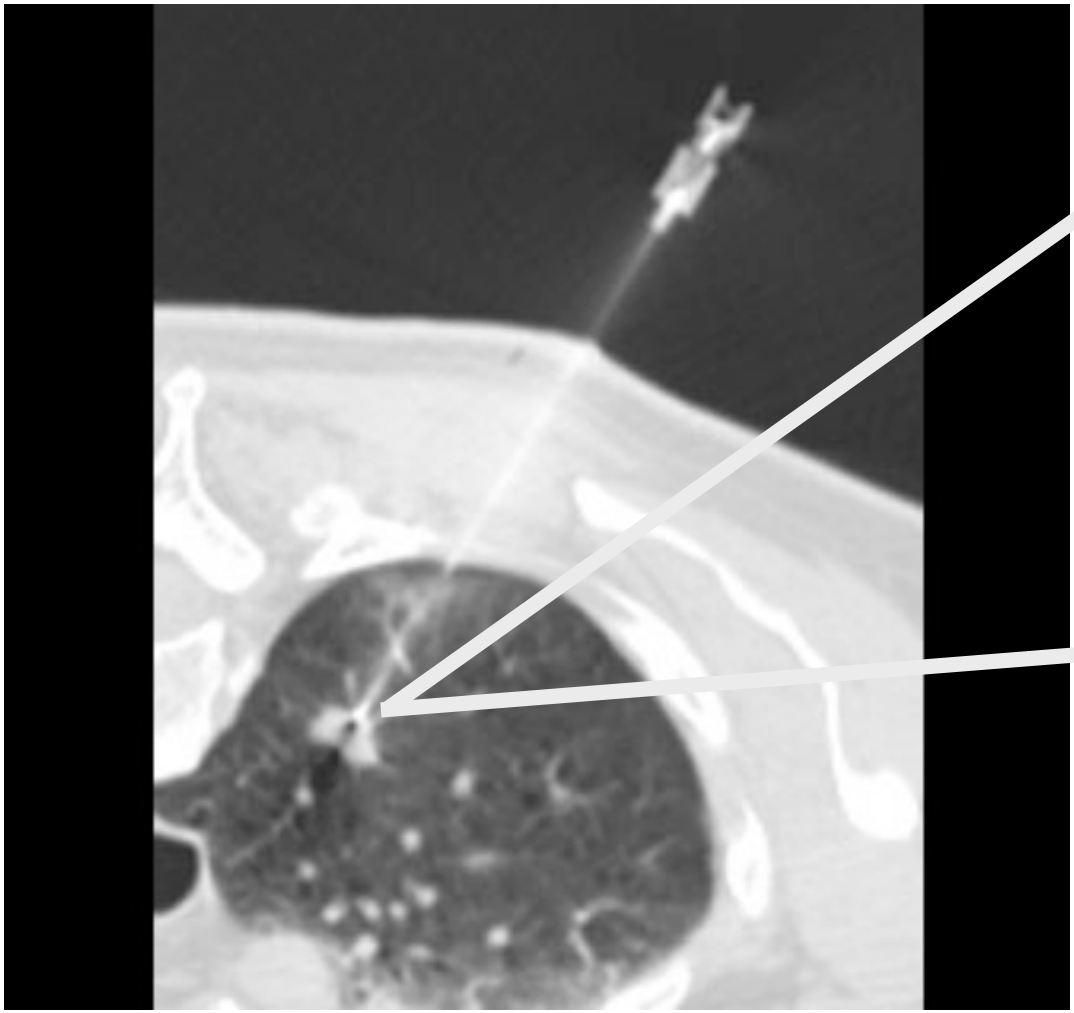
Fine- or courseneedle biopsi
from metastasis suspekte
areas (found by CT eller PET scan)

Not operabel

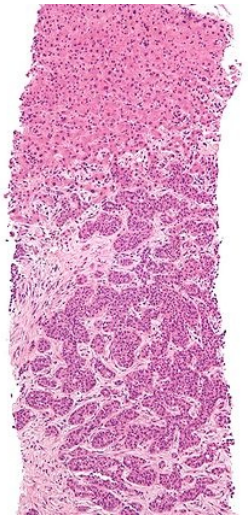
Operabel



CT guided needle biopsy

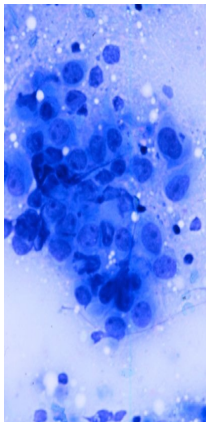


Coarse needle

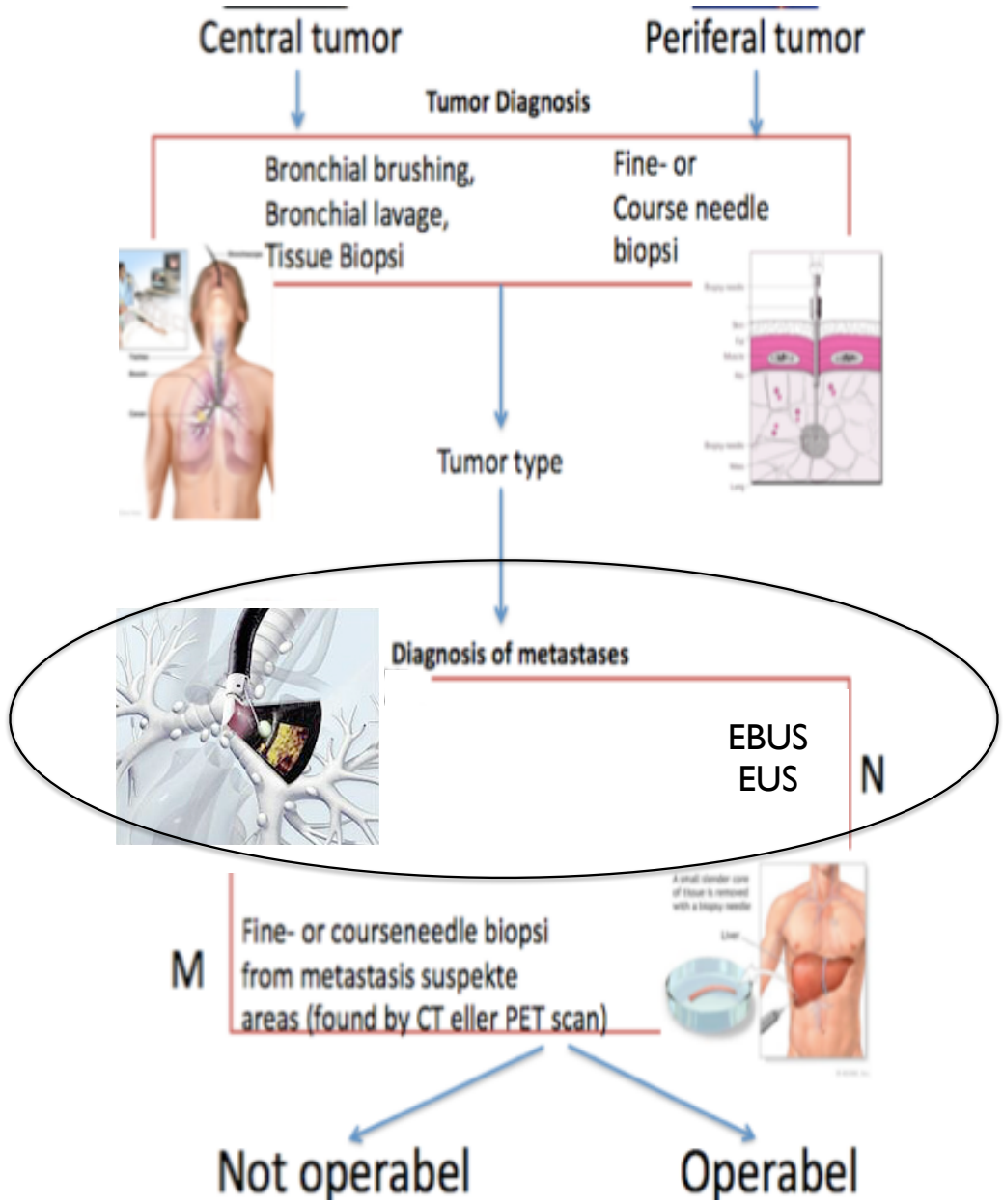


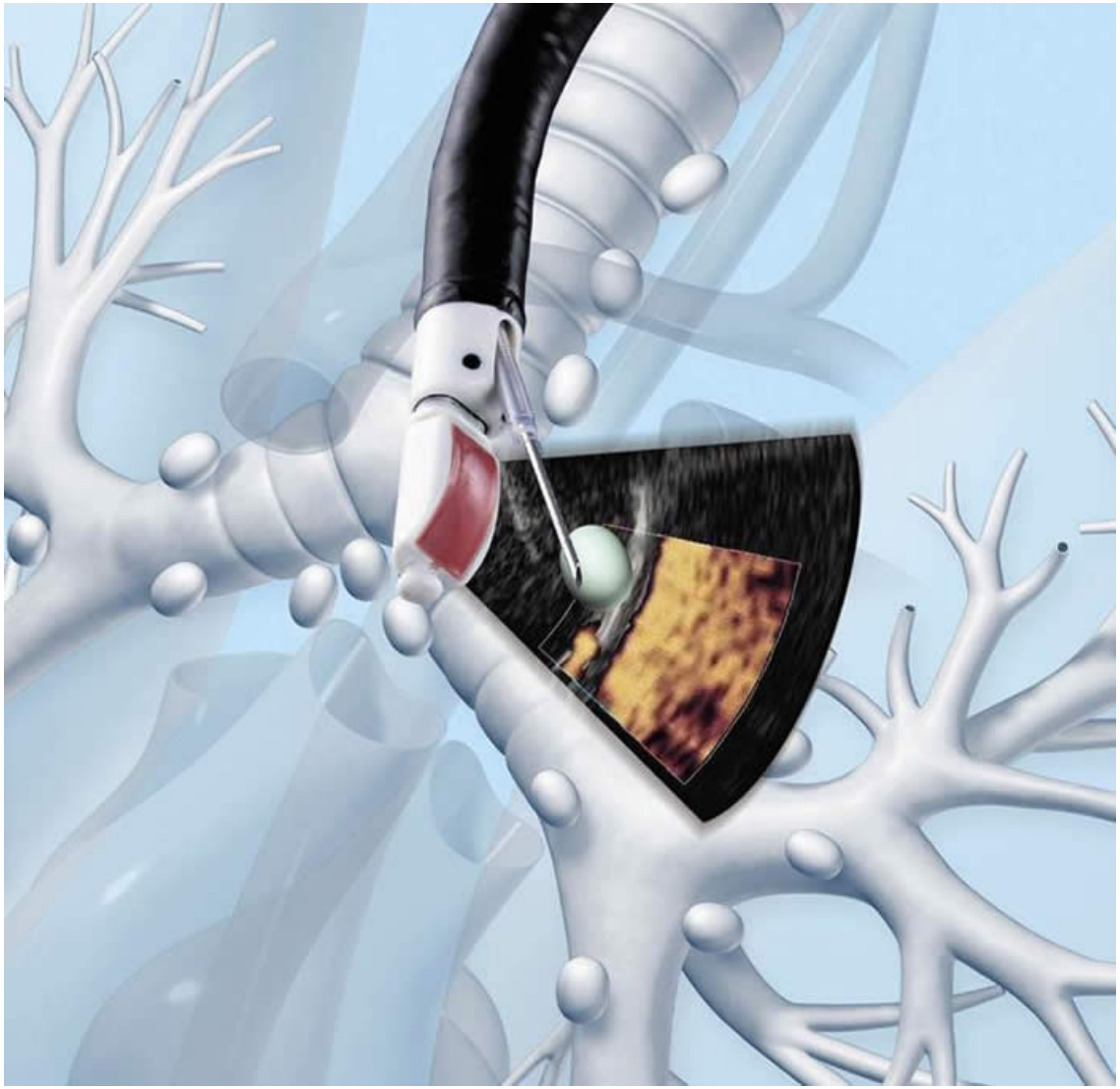
Histology

Fine needle



Cytology


Central tumor
Periferal tumor
Tumor Diagnosis
Bronchial brushing,
Bronchial lavage,
Tissue Biopsi
Fine- or
Course needle
biopsi
Tumor type
Diagnosis of metastases
EBUS
EUS
N
M
Fine- or courseneedle biopsi
from metastasis suspekte
areas (found by CT eller PET scan)
Not operabel
Operabel



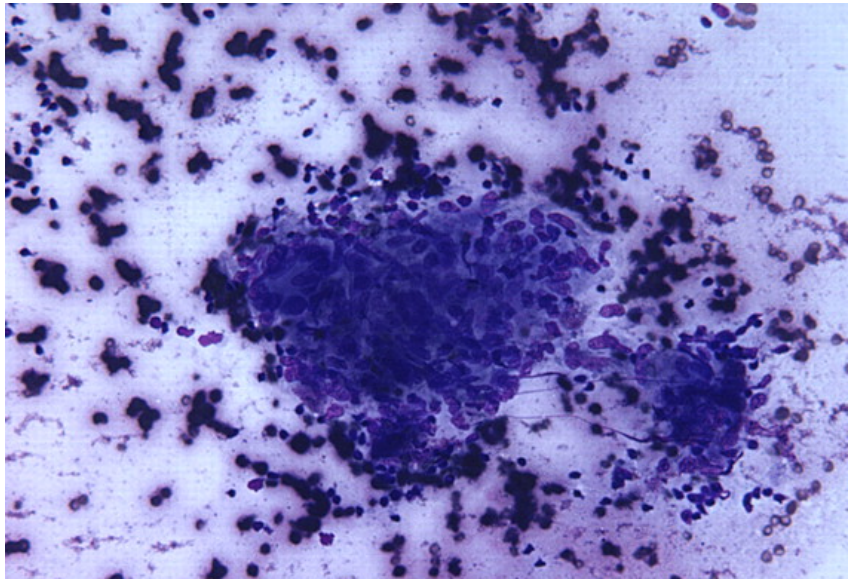
NordiQC

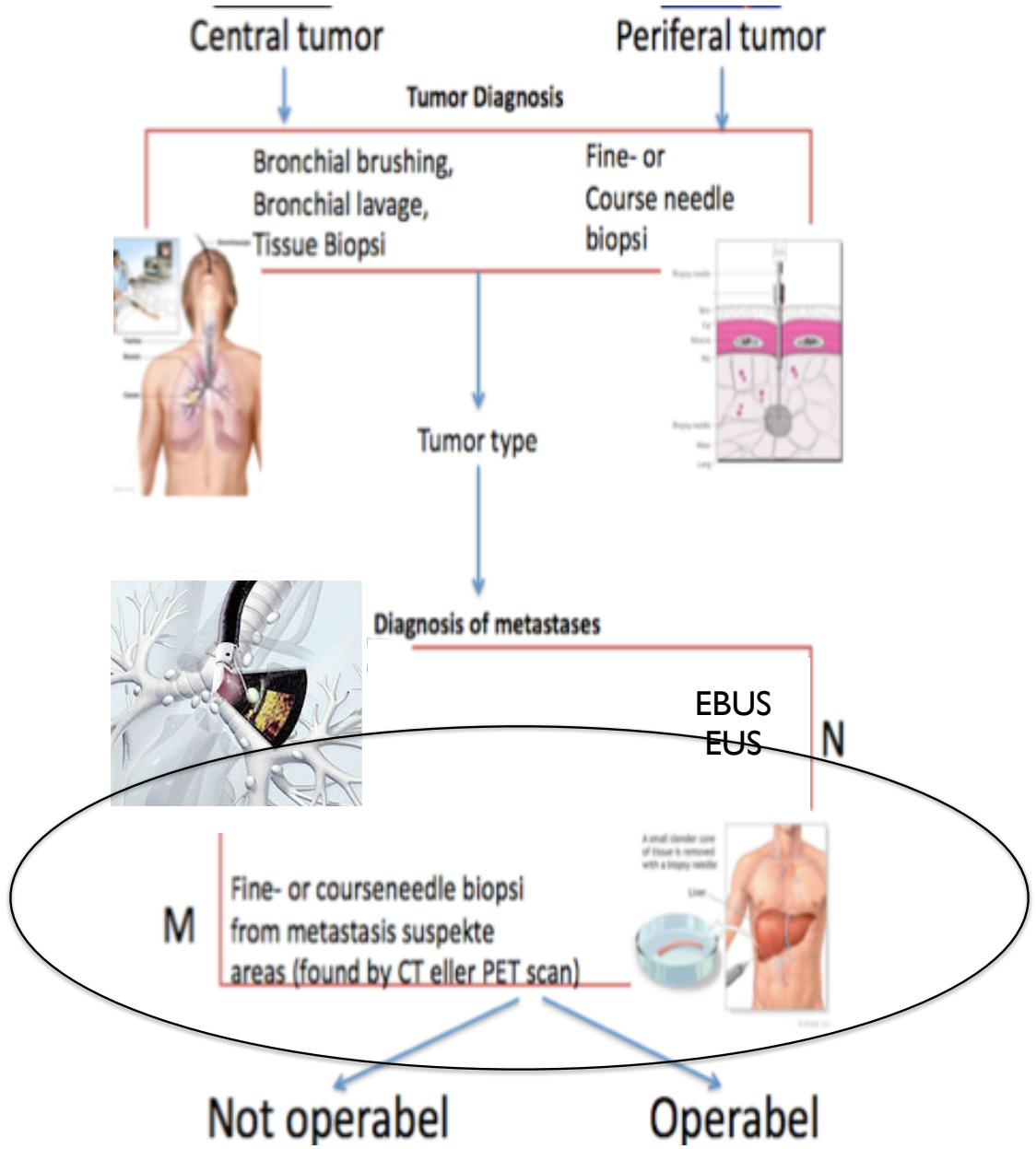
EBUS *Endobronchial Ultrasound Scanning*

EUS *Esophagal Ultraspund Scanning*

} TBNA

Cytology




Central tumor
Periferal tumor
Tumor Diagnosis
Bronchial brushing,
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Fine- or
Course needle
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Tumor type
Diagnosis of metastases
EBUS
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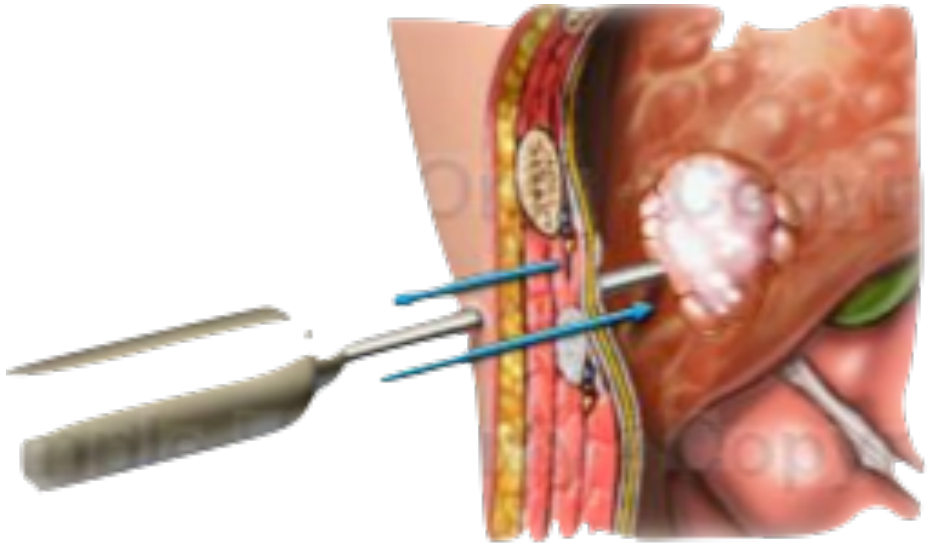
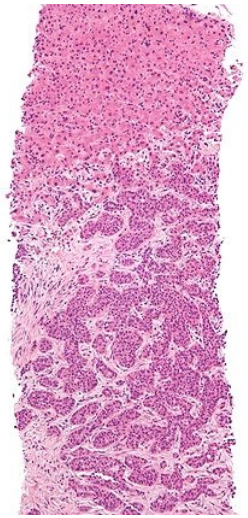
Fine- or courseneedle biopsi
from metastasis suspekte
areas (found by CT eller PET scan)
Not operabel
Operabel

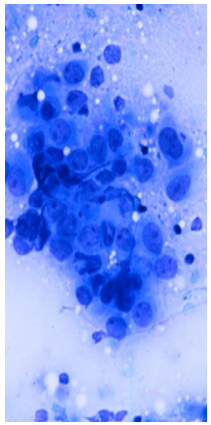


Coarse needle



Histology

Fine needle



Cytology

Patoanatomical specimen

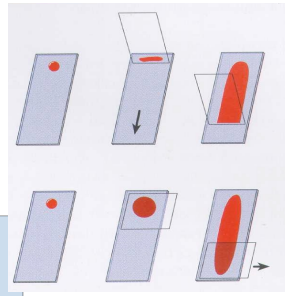
Histology

Cytologi

Fixation
Dehydration
Parafinembedding
Microtomy

Præparation

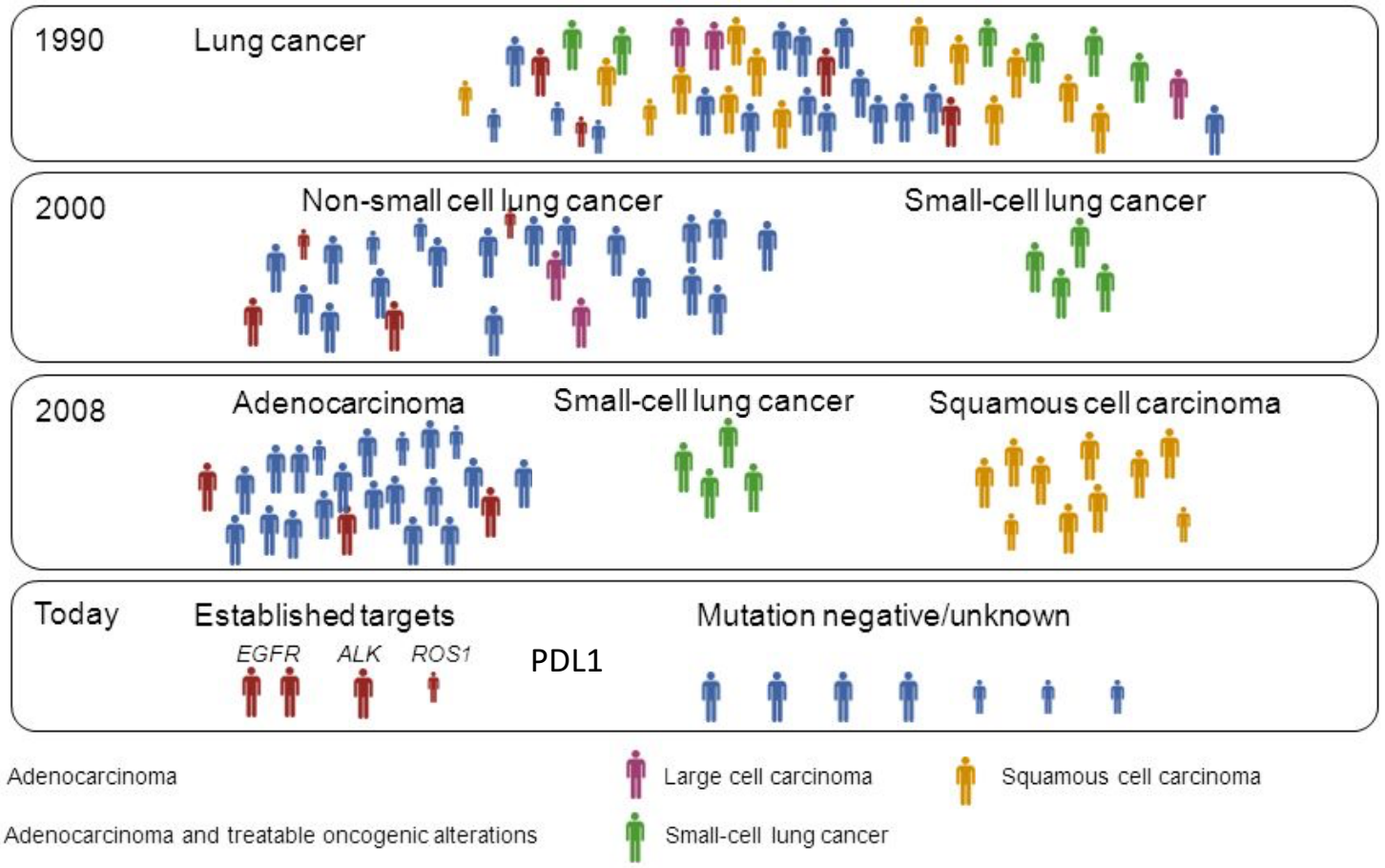
Smear preparation



Visualization

(Staining)

Patient selection in lung cancer: Evolution over time



Diagnosis

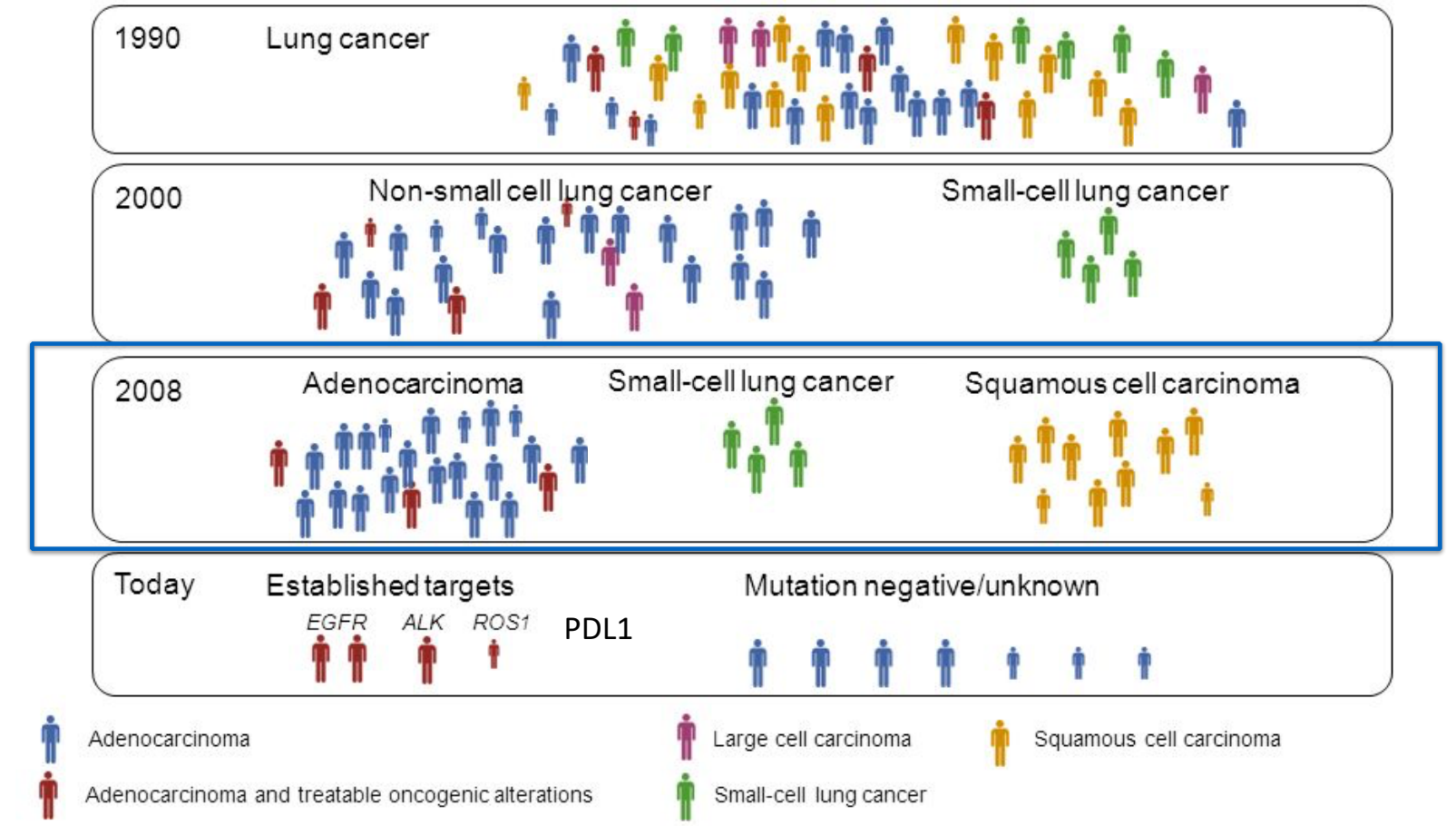
Diagnosis

Diagnosis

Prediction

Adapted from Reck M, et al. Lancet 2013;382:709–19

Patient selection in lung cancer: Evolution over time



Diagnosis

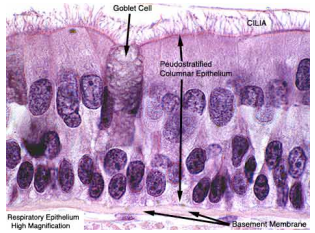
Diagnosis

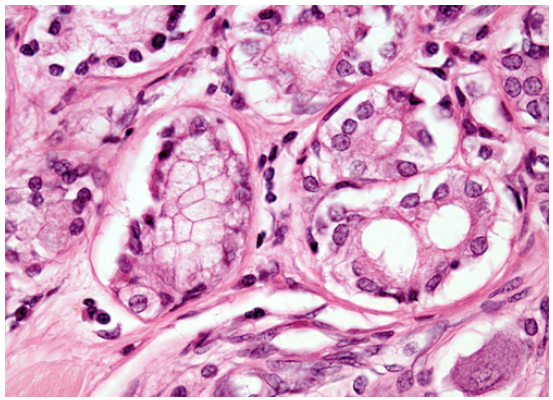
Diagnosis

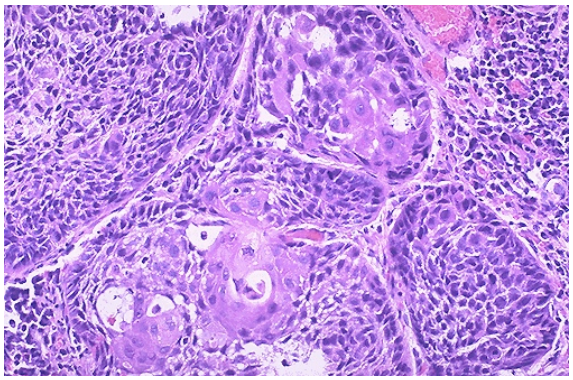
Prediction

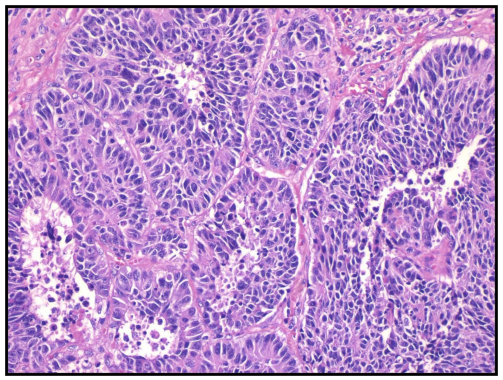
Adapted from Reck M, et al. Lancet 2013;382:709–19

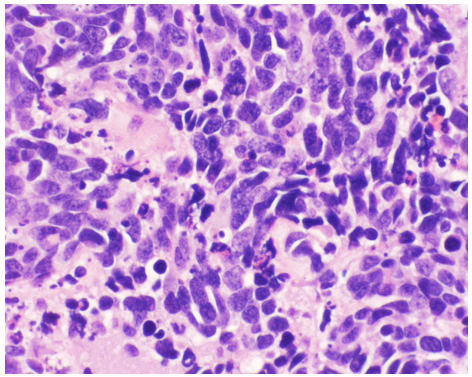
Morphology











Adenocarcinoma

Squamous carcinoma

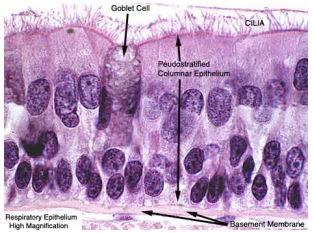
Large cell
neuroendocrine carc.

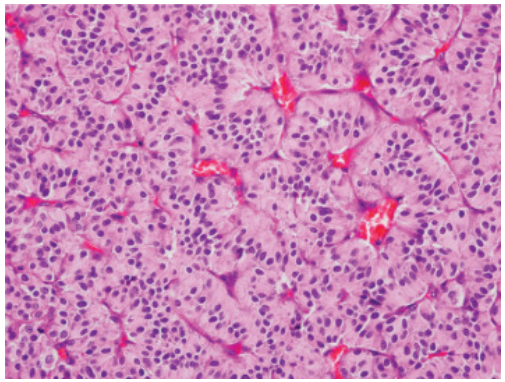
Small cell carcinoma

Non Small Cell Lung Carcinoma (NSCLC)

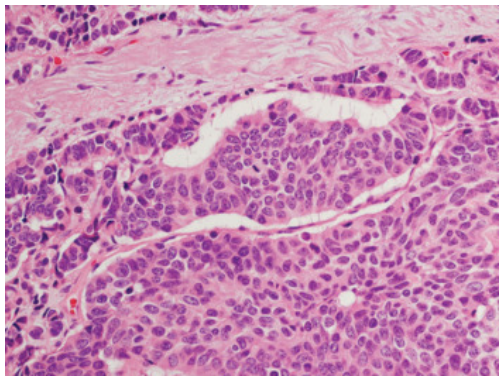
Neuroendocrine carcinoma

Morphology

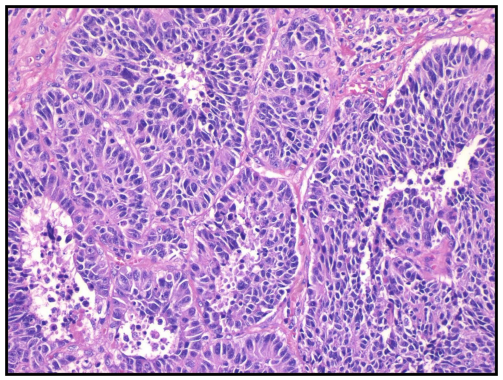




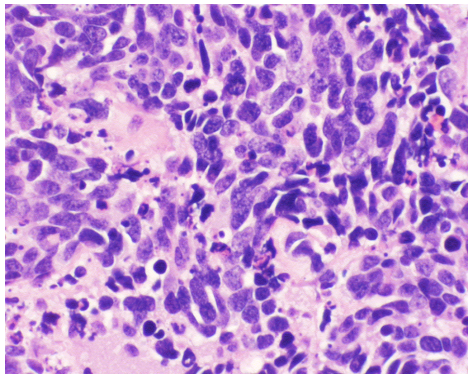
Typical carcinoid



Atypical carcinoid



Large cell
neuroendocrine carc.



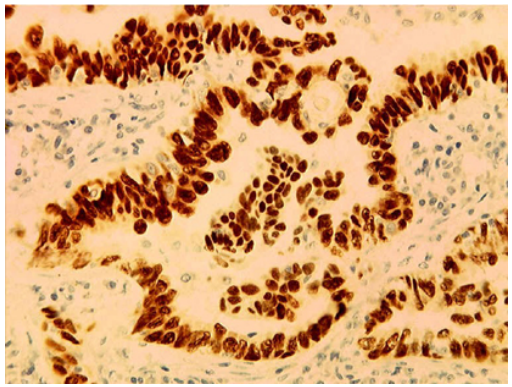
Small cell carcinoma

Neuroendocrine tumor

Neuroendocrine carcinoma

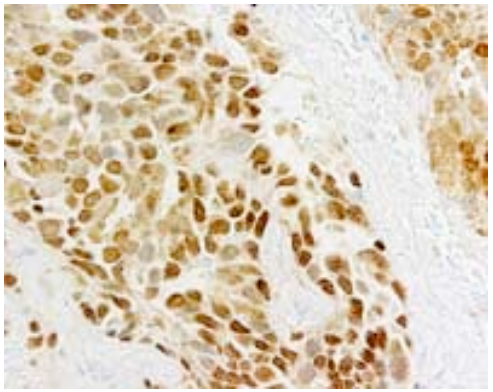
Immunohistochemistry

ttf1



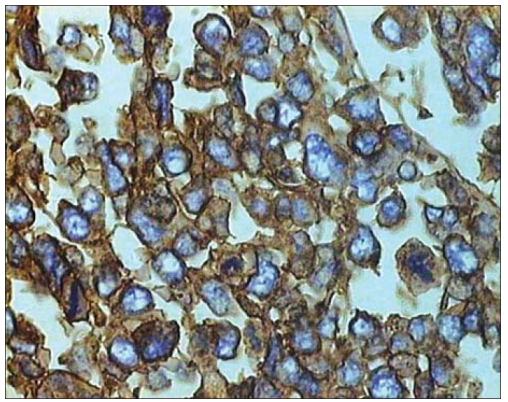
Adenocarcinoma

p63



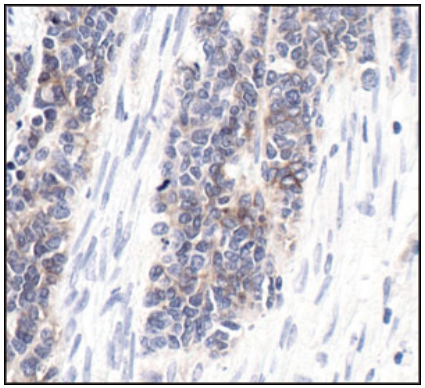
Squamous carcinoma

cd56



Large cell
neuroendocrine carc

cd56

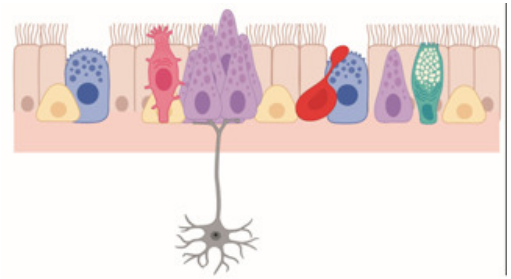


Small cell carcinoma

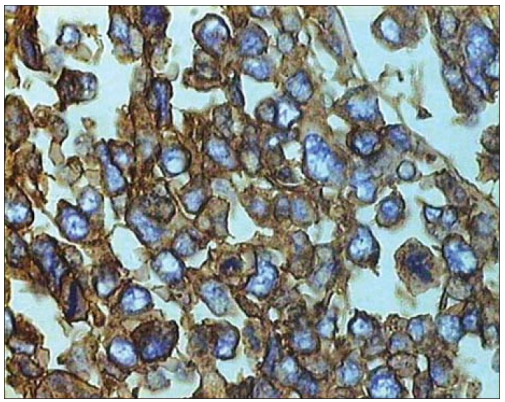
Non Small Cell Lung Carcinoma (NSCLC)

Neuroendocrine carcinoma

Immunohistochemistry

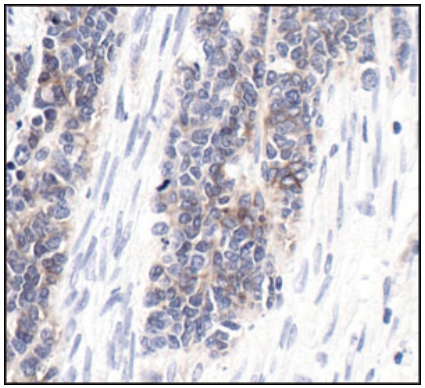


cd56

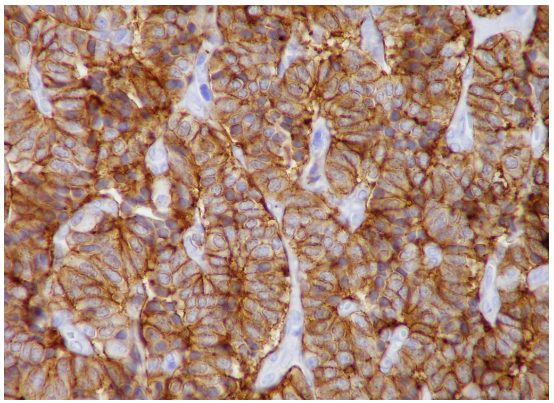


Large cell
neuroendocrine carc

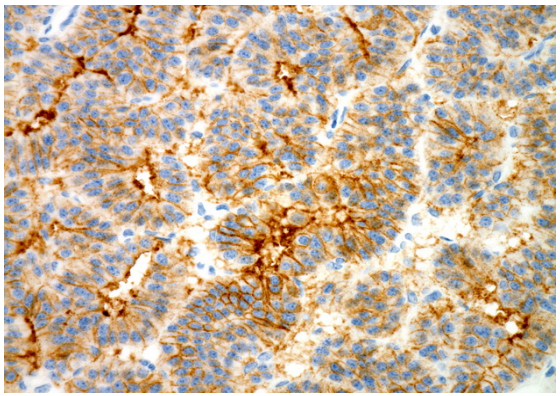
cd56



Small cell carcinoma



Typical carcinoid



Atypical carcinoid

Neuroendocrine tumor

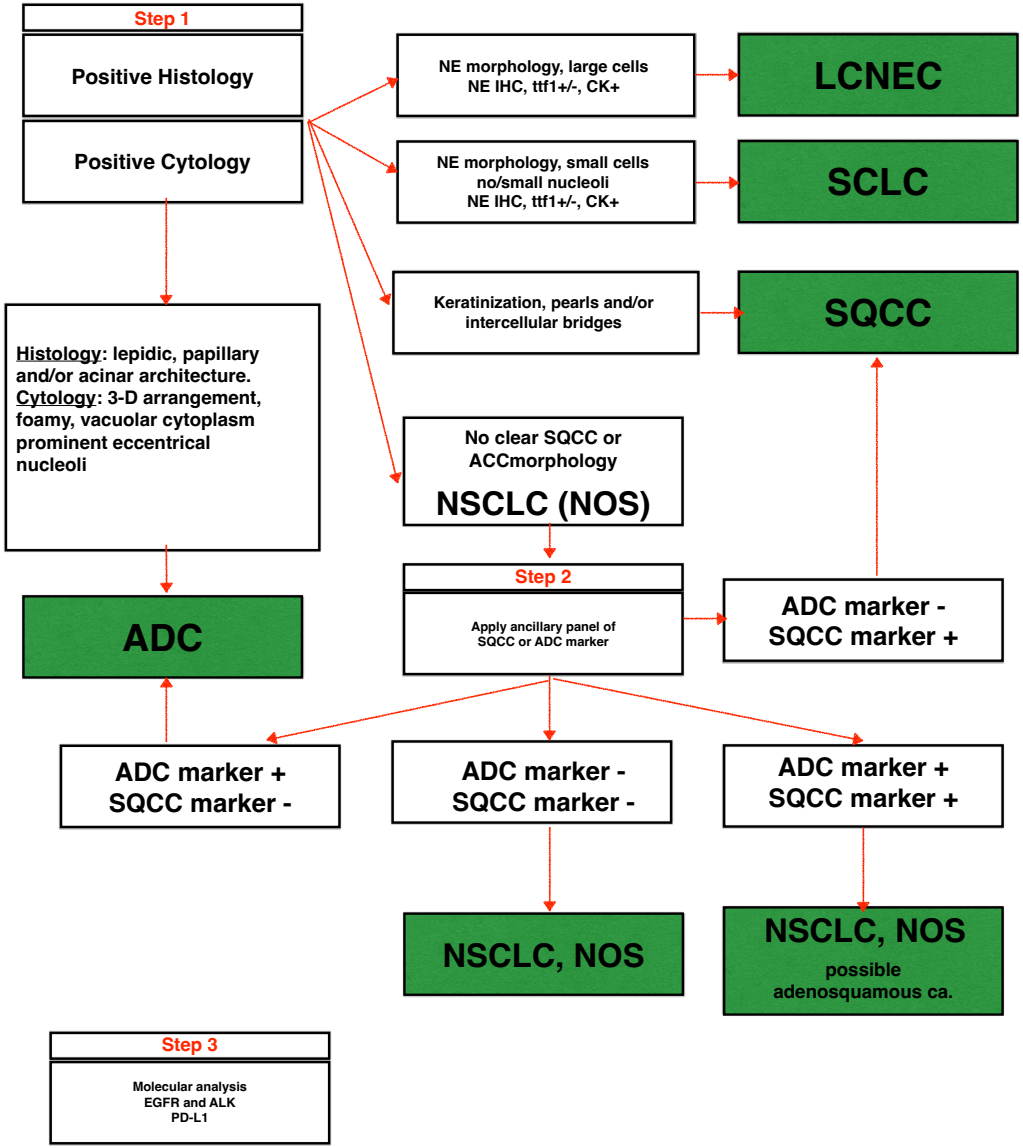
Neuroendocrine carcinoma

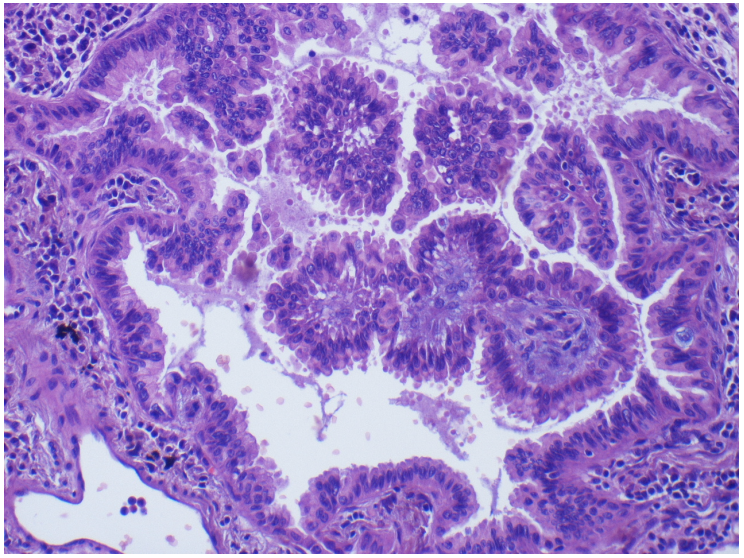
Algorithm modified from

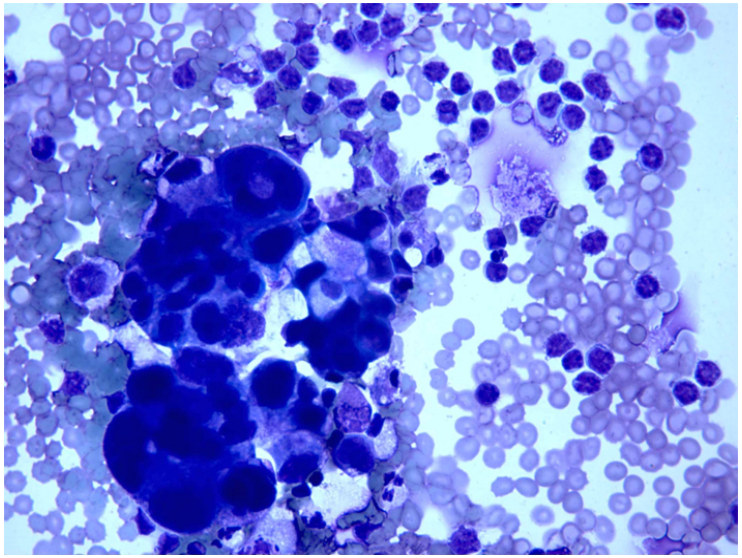
Diagnosis of Lung Cancer in Small Biopsies and Cytology

Implications of the 2011 International Association for the Study of Lung Cancer/ American Thoracic Society/European Respiratory Society Classification

William D. Travis, MD; Elisabeth Brambilla, MD; Masayuki Noguchi, MD; Andrew G. Nicholson, DM; Kim Geisinger, MD; Yasushi Yatabe, MD; Yuichi Ishikawa, MD; Ignacio Wistuba, MD; Douglas B. Flieder, MD; Wilbur Franklin, MD; Adi Cagatay, MD; Philip S. Hasleton, MD; Douglas W. Henderson, MD; Keith M. Kerr, MD; Iver Petersen, MD; Victor Roggli, MD; Erik Thunnissen, MD; Ming Tsao, MD







Step 1

Positive Histology

Positive Cytology

Histology: lepidic, papillary and/or acinar architecture.
Cytology: 3-D arrangement, foamy, vacuolar cytoplasm prominent eccentrical nucleoli

ADC

NE morphology, large cells
NE IHC, ttf1+/-, CK+
LCNEC

NE morphology, small cells
no/small nucleoli
NE IHC, ttf1+/-, CK+
SCLC

Keratinization, pearls and/or intercellular bridges
SQCC

No clear SQCC or ACCmorphology
NSCLC (NOS)

Step 2

Apply ancillary panel of SQCC or ADC marker

ADC marker - SQCC marker +

ADC marker + SQCC marker -

ADC marker - SQCC marker -

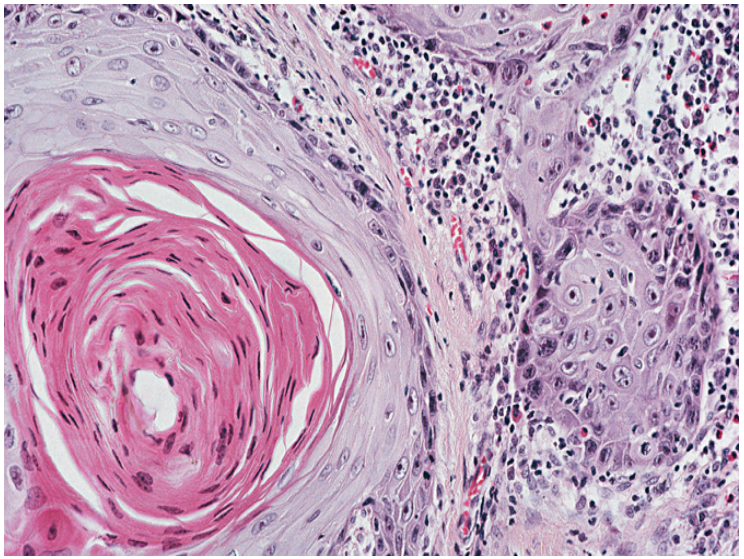
ADC marker + SQCC marker +

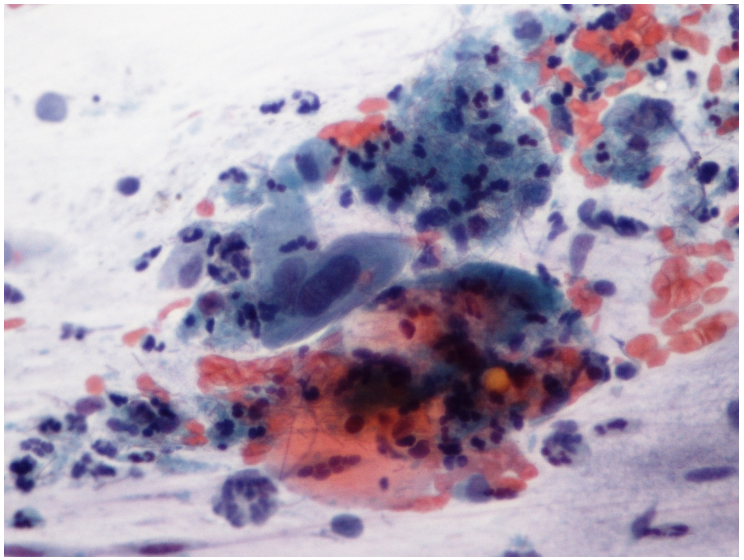
NSCLC, NOS

NSCLC, NOS
possible adenosquamous ca.

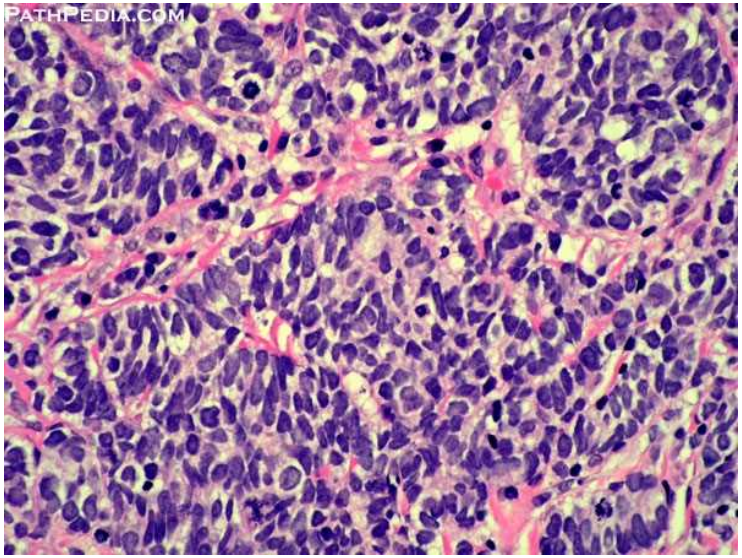
Step 3

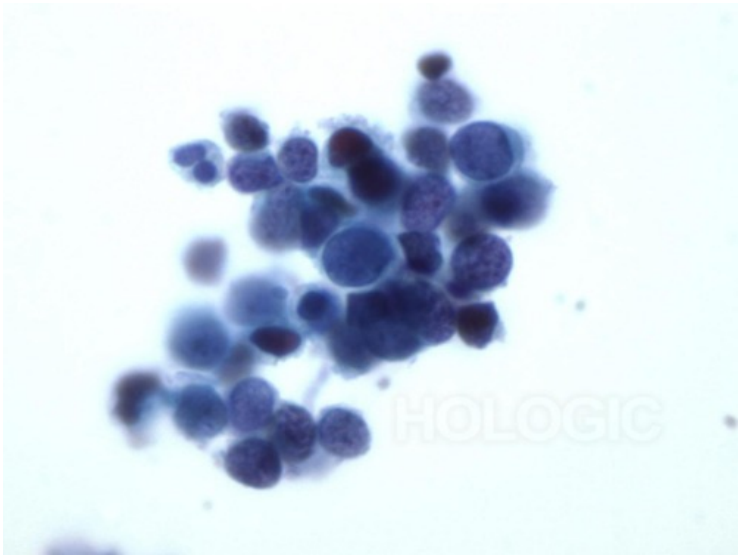
Molecular analysis
EGFR and ALK



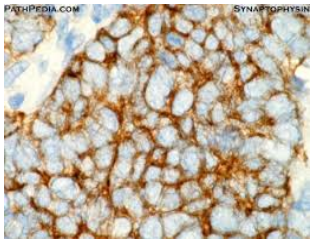



Step 1
Positive Histology
Positive Cytology
NE morphology, large cells
NE IHC, ttf1+/-, CK+
LCNEC
NE morphology, small cells
no/small nucleoli
NE IHC, ttf1+/-, CK+
SCLC
Keratinization, pearls and/or intercellular bridges
SQCC
Histology: lepidic, papillary and/or acinar architecture.
Cytology: 3-D arrangement, foamy, vacuolar cytoplasm prominent eccentrical nucleoli
No clear SQCC or ACCmorphology
NSCLC (NOS)
Step 2
Apply ancillary panel of SQCC or ADC marker
ADC marker - SQCC marker +
ADC
ADC marker + SQCC marker -
ADC marker - SQCC marker -
ADC marker + SQCC marker +
NSCLC, NOS
NSCLC, NOS
possible adenosquamous ca.
Step 3
Molecular analysis
EGFR and ALK

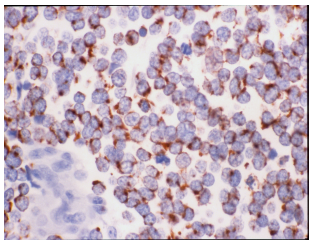

PATHPEDIA.COM


HOLOGIC

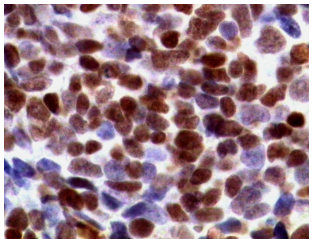

Step 1
Positive Histology
Positive Cytology
NE morphology, large cells
NE IHC, ttf1+/-, CK+
LCNEC
NE morphology, small cells
no/small nucleoli
NE IHC, ttf1+/-, CK+
SCLC
Histology: lepidic, papillary and/or acinar architecture.
Cytology: 3-D arrangement, foamy, vacuolar cytoplasm prominent eccentrical nucleoli
Keratinization, pearls and/or intercellular bridges
SQCC
No clear SQCC or ACCmorphology
NSCLC (NOS)
Step 2
Apply ancillary panel of SQCC or ADC marker
ADC marker - SQCC marker +
ADC
ADC marker + SQCC marker -
ADC marker - SQCC marker -
ADC marker + SQCC marker +
NSCLC, NOS
NSCLC, NOS
possible adenosquamous ca.
Step 3
Molecular analysis EGFR and ALK



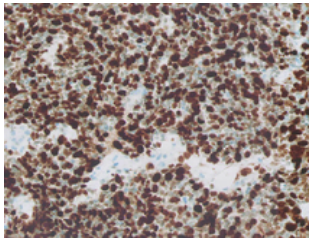
Neuroendocrine marker



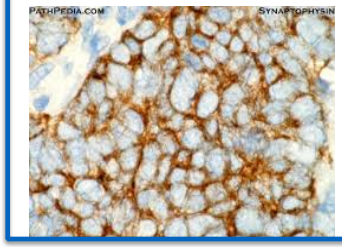
Cytokeratin



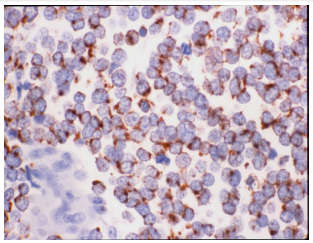
ttf1



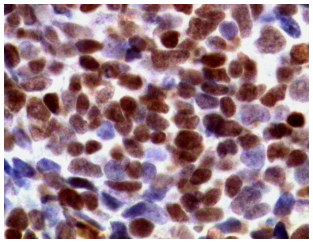
Ki67



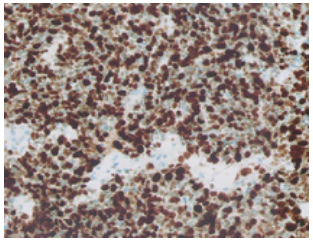
Neuroendocrine marker



Cytokeratin



ttf1

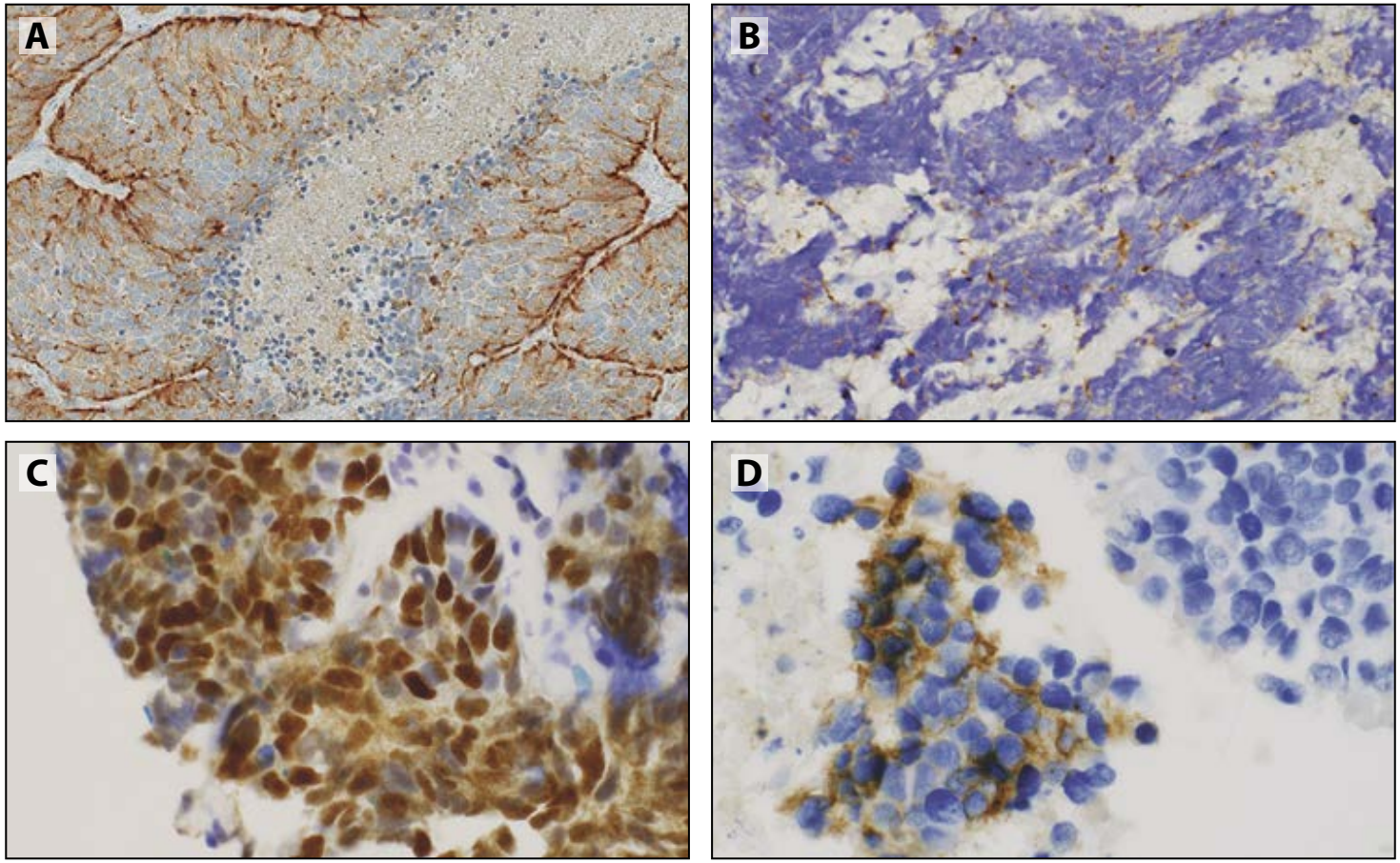


Ki67

Neuroendocrine markers

Chromogranin A

Synaptofycin



INSM1 Insulinoma-Associated Protein 1

CD56

IASLC ATLAS OF DIAGNOSTIC IMMUNOHISTOCHEMISTRY

Neuroendocrine markers

Sensitivity

Entity	Overall Cases Analyzed (N)	Positive Cases [n (%)]*				
		INSM1	SYN	CHRA	CD56	Any Conventional (SYN/CHRA/CD56)
LCNEC	77	32 (42)	47 (61)	32 (42)	66 (86)	70 (91)
SCLC	144	124 (86)	122 (85)	107 (74)	132 (92)	137 (95)

Insulinoma-associated Protein 1 (INSM1) in Thoracic Tumors is Less Sensitive but More Specific Compared With Synaptophysin, Chromogranin A, and CD56

Katharina Kriegsmann, MD, MBA, Christiane Zgorzelski,† Daniel Kazdal, PhD,†‡ Martin Cremer, MD,* Thomas Muley, PhD,§‖ Hauke Winter, MD, PhD,‡‖ Rémi Longuespée, PhD,† Jörg Kriegsmann, MD, PhD,¶ Arne Warth, MD, PhD,# and Mark Kriegsmann, MD†*

Neuroendocrine markers

Specificity

Entity	Overall Cases Analyzed (N)	Positive Cases [n (%)]*				
		INSM1	SYN	CHRA	CD56	Any Conventional (SYN/CHRA/CD56)
ADC	47	1 (2)	6 (13)	4 (9)	7 (15)	10 (21)
SqCC	44	0 (0)	2 (5)	0 (0)	9 (20)	10 (23)

Insulinoma-associated Protein 1 (INSM1) in Thoracic Tumors is Less Sensitive but More Specific Compared With Synaptophysin, Chromogranin A, and CD56

Katharina Kriegsmann, MD, MBA, Christiane Zgorzelski,† Daniel Kazdal, PhD,†‡ Martin Cremer, MD,* Thomas Muley, PhD,§‖ Hauke Winter, MD, PhD,‡‖ Rémi Longuespée, PhD,† Jörg Kriegsmann, MD, PhD,¶ Arne Warth, MD, PhD,# and Mark Kriegsmann, MD†*

Neuroendocrine markers

Specificity

Entity	Overall Cases Analyzed (N)	Positive Cases [n (%)]*				
		INSM1	SYN	CHRA	CD56	Any Conventional (SYN/CHRA/CD56)
ADC	47	1 (2)	6 (13)	4 (9)	7 (15)	10 (21)
SqCC	44	0 (0)	2 (5)	0 (0)	9 (20)	10 (23)

Insulinoma-associated Protein 1 (INSM1) in Thoracic Tumors is Less Sensitive but More Specific Compared With Synaptophysin, Chromogranin A, and CD56

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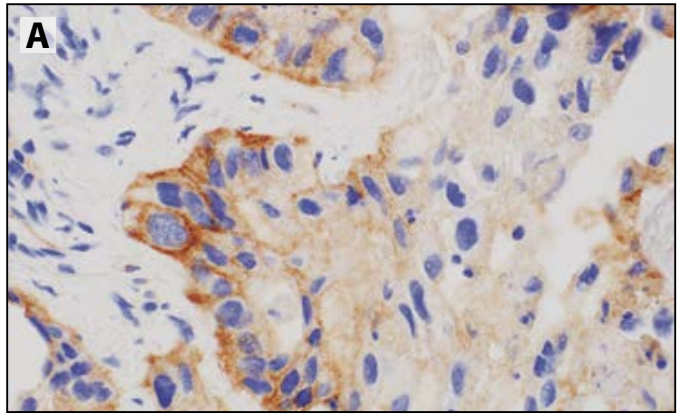
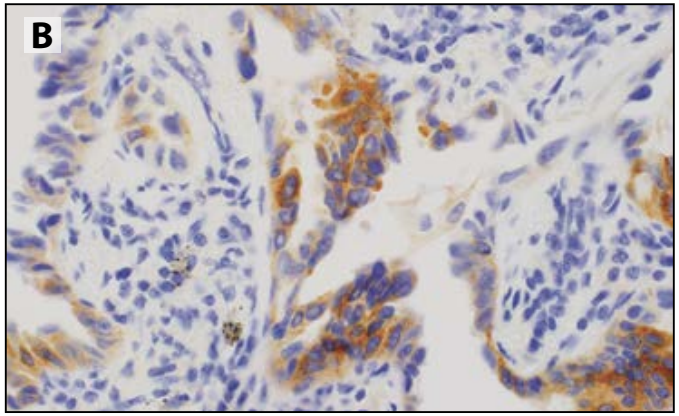
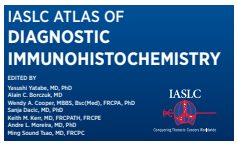


SqCC, CD56



ADC, syn

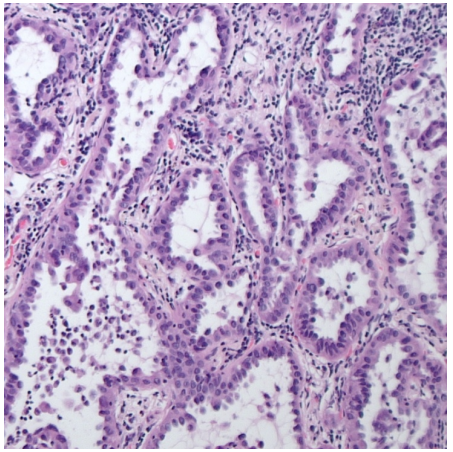


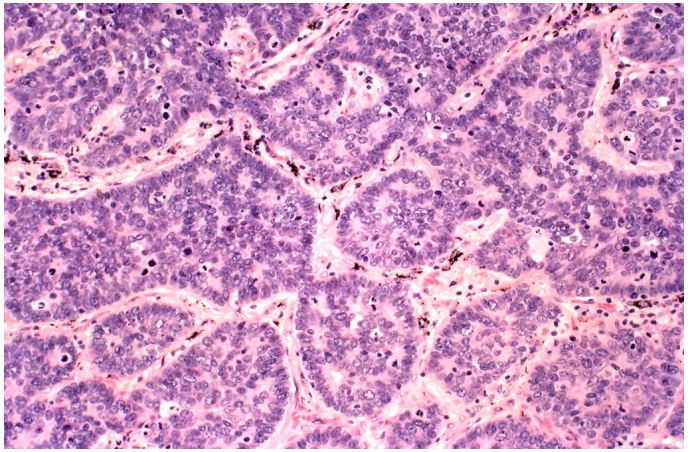
Neuroendocrine markers

Specificity

Entity	Overall Cases Analyzed (N)	Positive Cases [n (%)]*				
		INSM1	SYN	CHRA	CD56	Any Conventional (SYN/CHRA/CD56)
ADC	47	1 (2)	6 (13)	4 (9)	7 (15)	10 (21)
SqCC	44	0 (0)	2 (5)	0 (0)	9 (20)	10 (23)

Morphology





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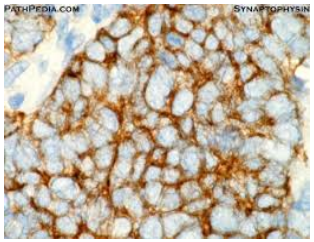
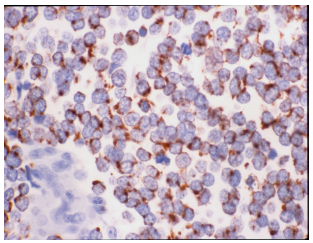
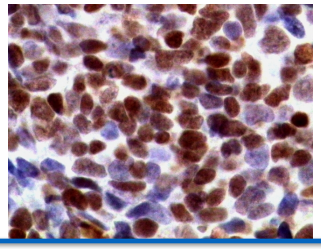


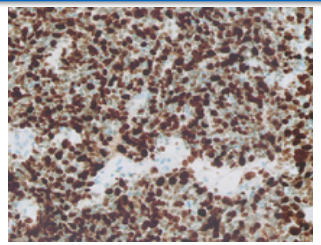
Neuroendocrine marker



Cytokeratin



ttf1



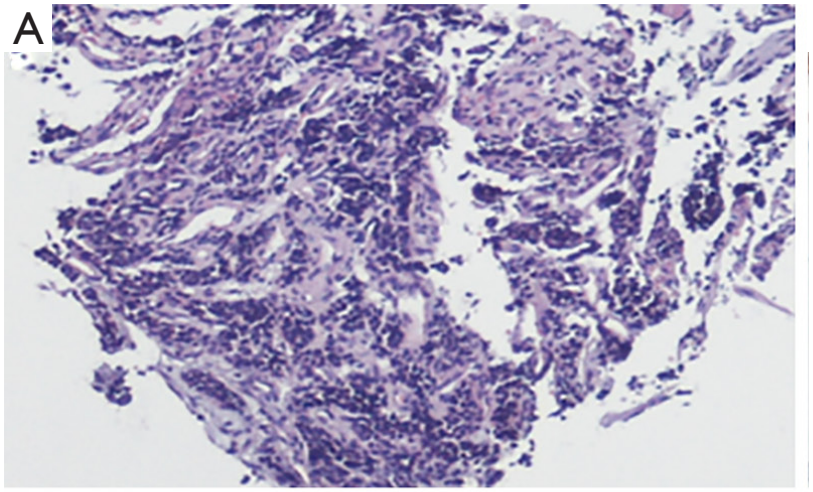
Ki67

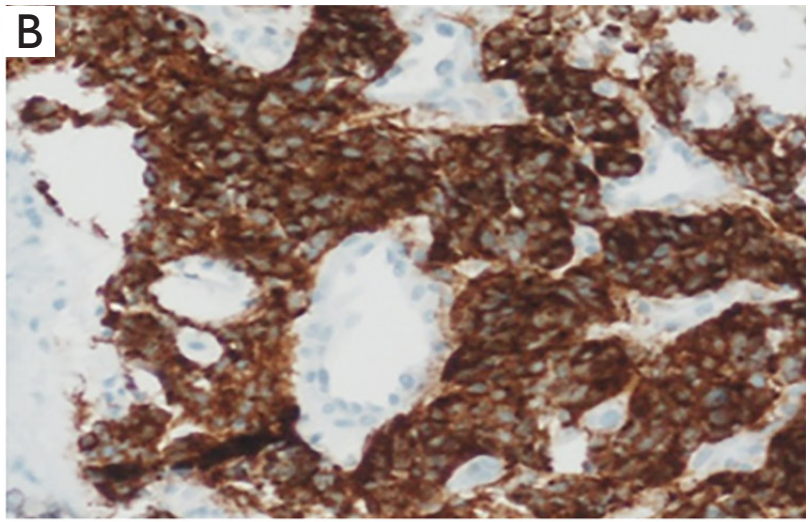
Neuroendocrine markers

Case Report

Erroneous diagnosis of small cell lung cancer based on small biopsies with far-reaching consequences: case report of a typical carcinoid tumor

Ioannis Kyritsis[1], Bettina Krebs[1], Sandra Kampe[2], Dirk Theegarten[3], Clemens Aigner[1], Stefan Welter[1]





Neuroendocrine markers

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Erroneous diagnosis of small cell lung cancer based on small biopsies with far-reaching consequences: case report of a typical carcinoid tumor

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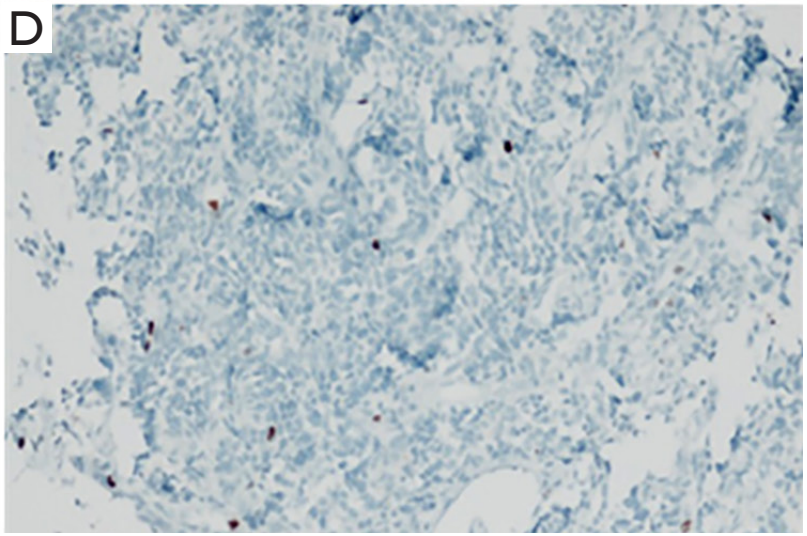

Ki67, re-evaluation

Neuroendocrine markers

Specificity

Entity	Overall Cases Analyzed (N)	Positive Cases [n (%)]*				
		INSM1	SYN	CHRA	CD56	Any Conventional (SYN/CHRA/CD56)
Typical carcinoid	112	91 (81)	111 (99)	111 (99)	112 (100)	112 (100)
Atypical carcinoid	39	29 (74)	39 (100)	39 (100)	39 (100)	39 (100)

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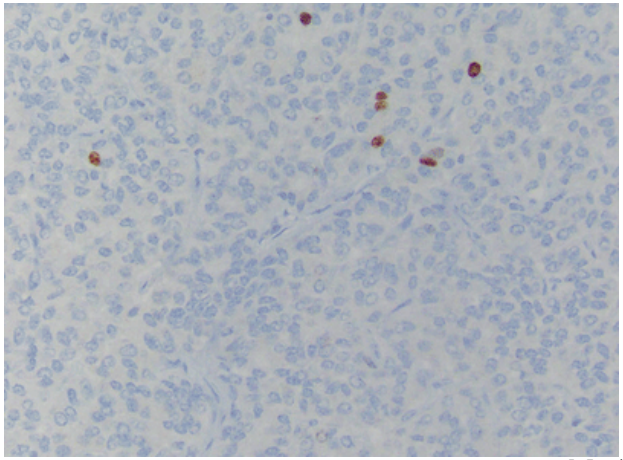
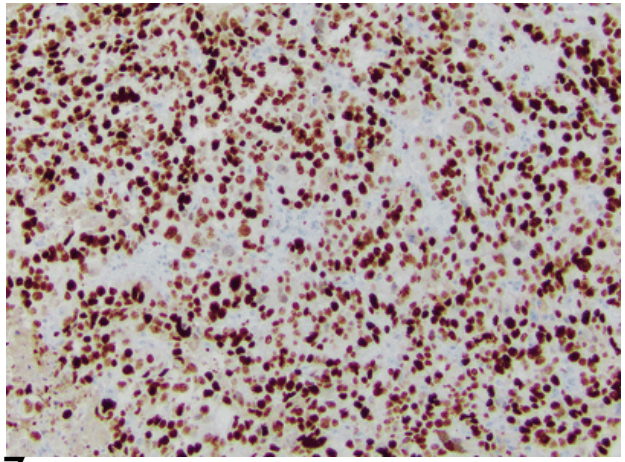
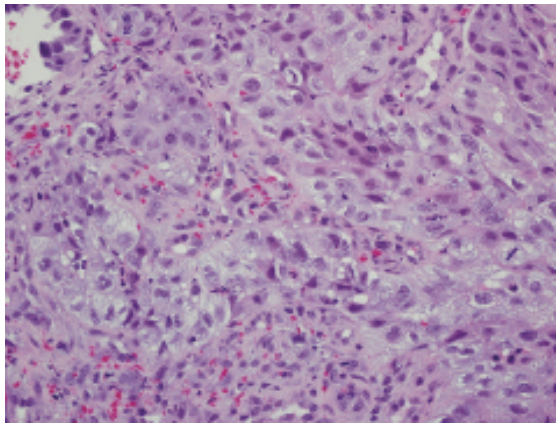


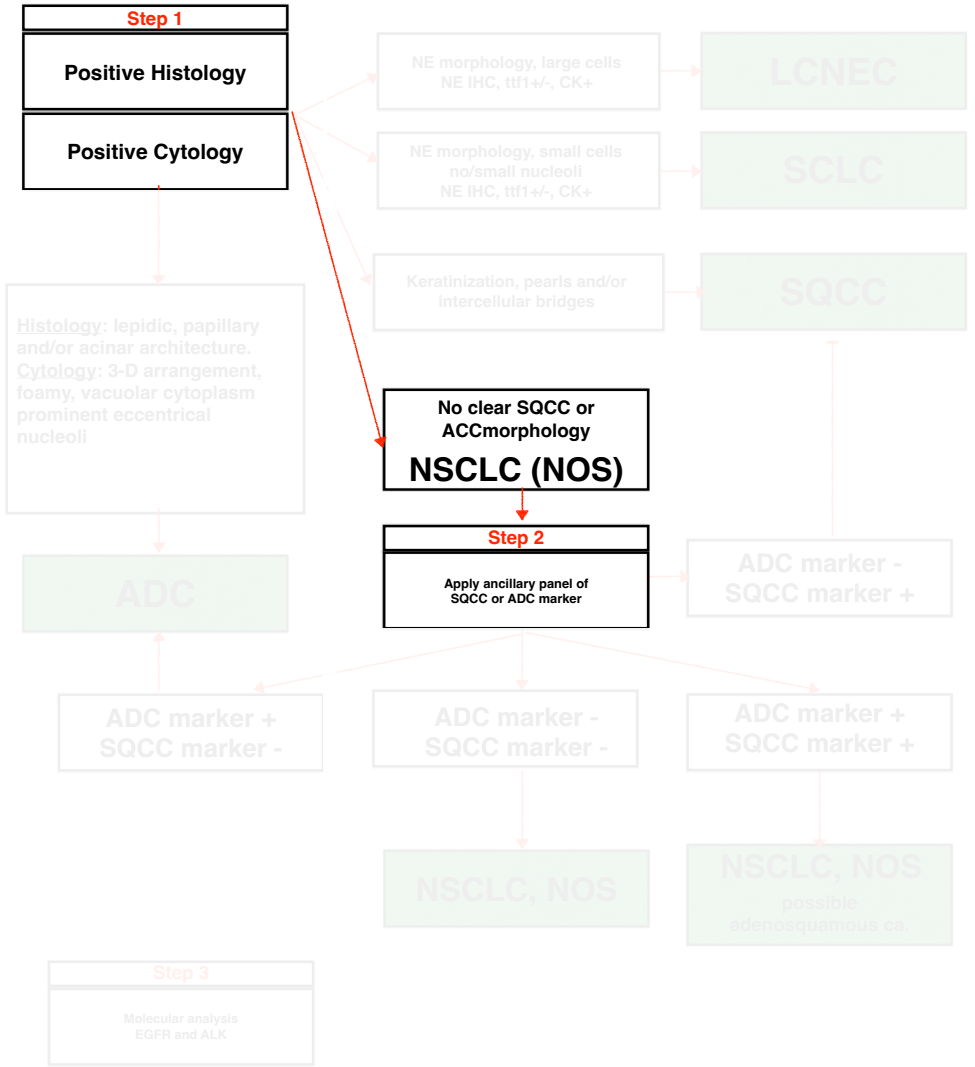
Carcinoid

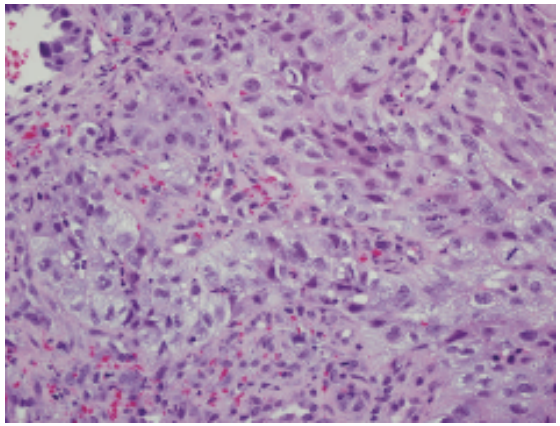
Ki67

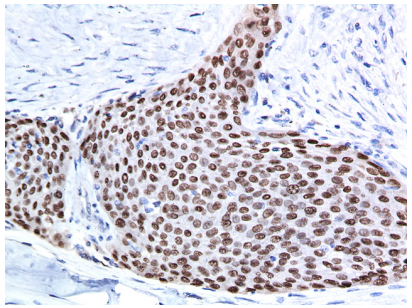


SCLC



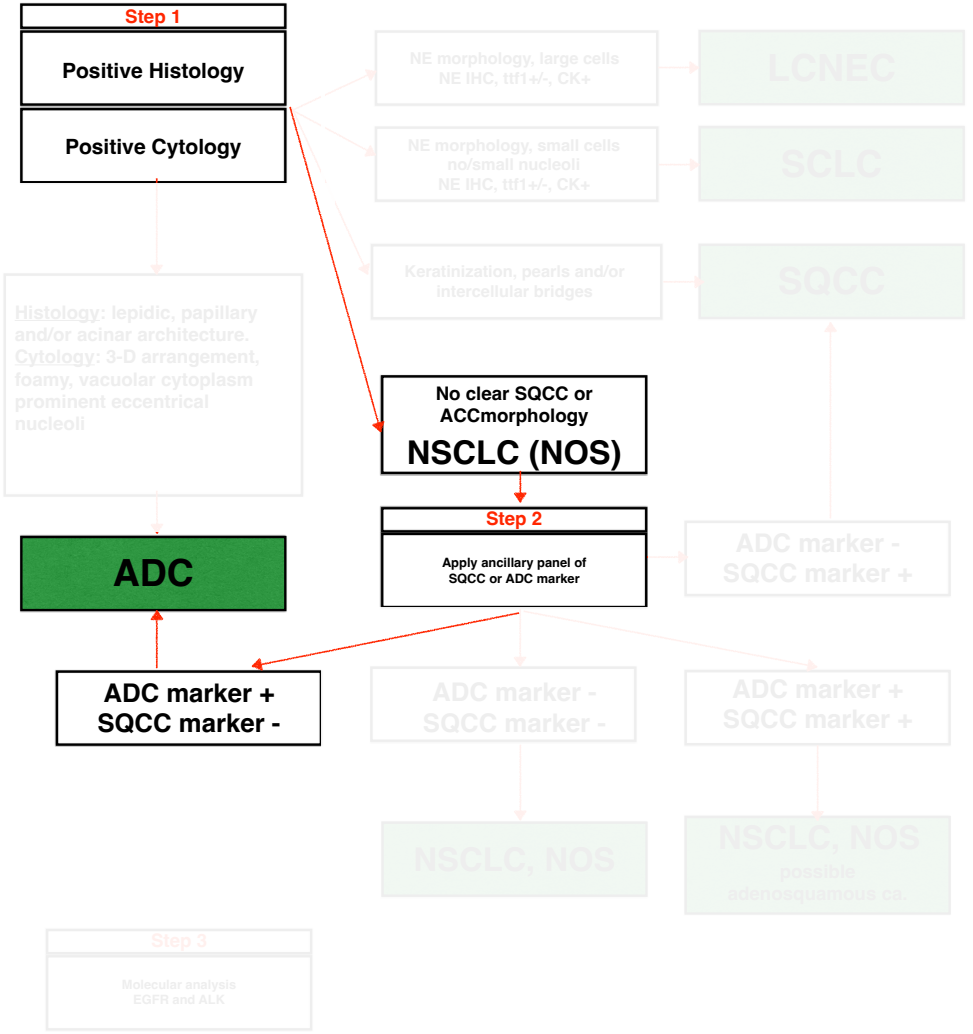

Step 1
Positive Histology
Positive Cytology
NE morphology, large cells
NE IHC, ttf1+/-, CK+
LCNEC
NE morphology, small cells
no/small nucleoli
NE IHC, ttf1+/-, CK+
SCLC
Keratinization, pearls and/or
intercellular bridges
SQCC
Histology: lepidic, papillary
and/or acinar architecture.
Cytology: 3-D arrangement,
foamy, vacuolar cytoplasm
prominent eccentrical
nucleoli
No clear SQCC or
ACCmorphology
NSCLC (NOS)
Step 2
Apply ancillary panel of
SQCC or ADC marker
ADC marker -
SQCC marker +
ADC
ADC marker +
SQCC marker -
ADC marker -
SQCC marker -
ADC marker +
SQCC marker +
NSCLC, NOS
NSCLC, NOS
possible
adenosquamous ca.
Step 3
Molecular analysis
EGFR and ALK

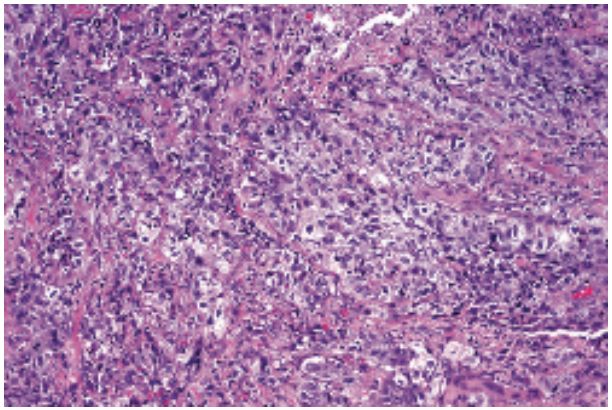


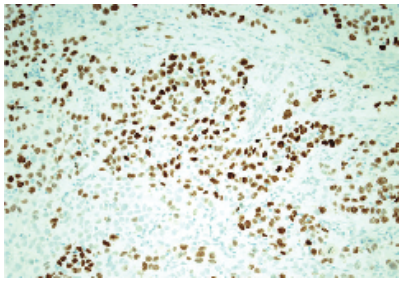


ttf l +

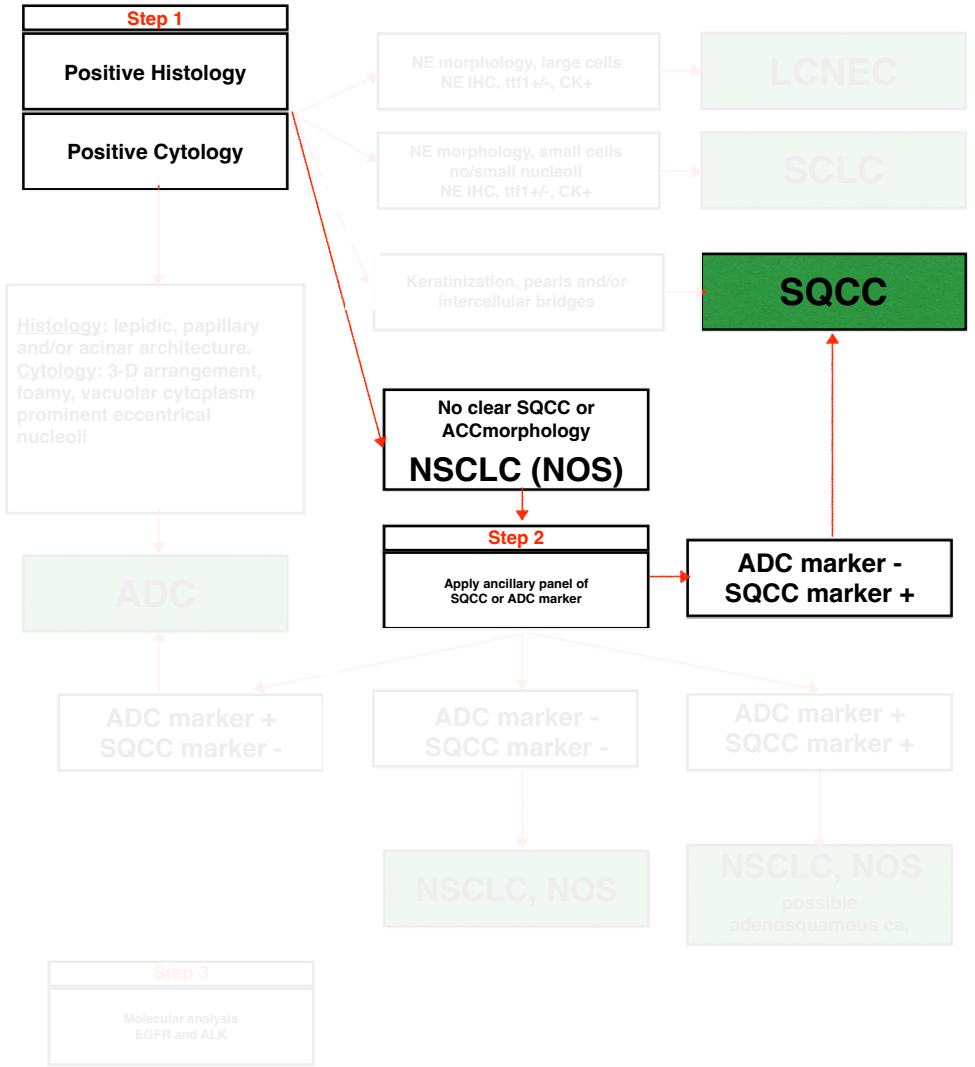
(+Cytokeratin 7)

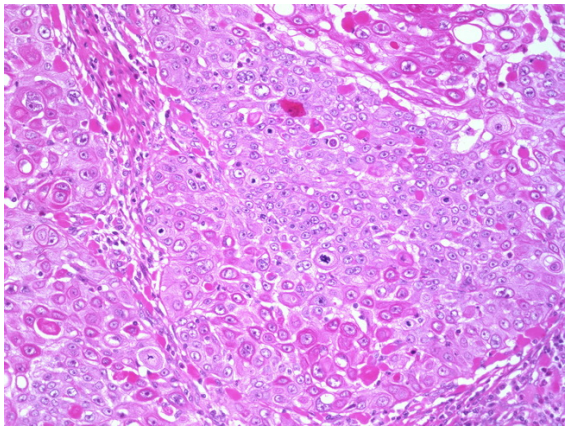


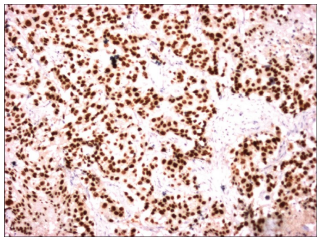




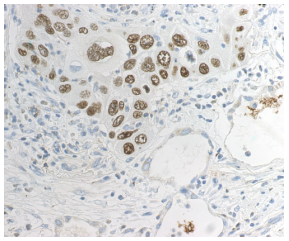
P63+ (+Cytokeratin 5/6)



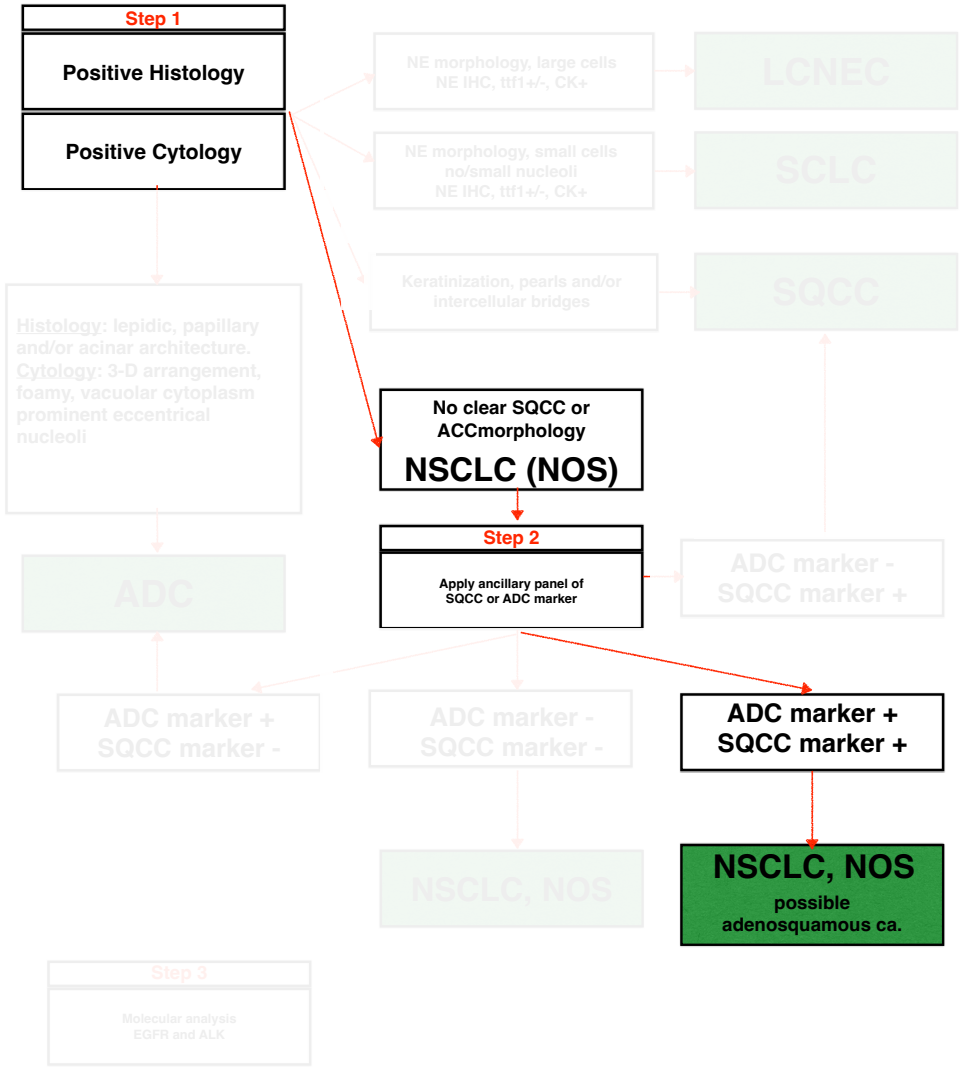




ttf1+



P63+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Keratinization, pearls and/or
intercellular bridges
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Histology: lepidic, papillary
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prominent eccentrical
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No clear SQCC or
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Step 2
Apply ancillary panel of
SQCC or ADC marker
ADC marker -
SQCC marker +
ADC
ADC marker +
SQCC marker -
ADC marker -
SQCC marker -
ADC marker +
SQCC marker +
NSCLC, NOS
possible
adenosquamous ca.
NSCLC, NOS
Step 3
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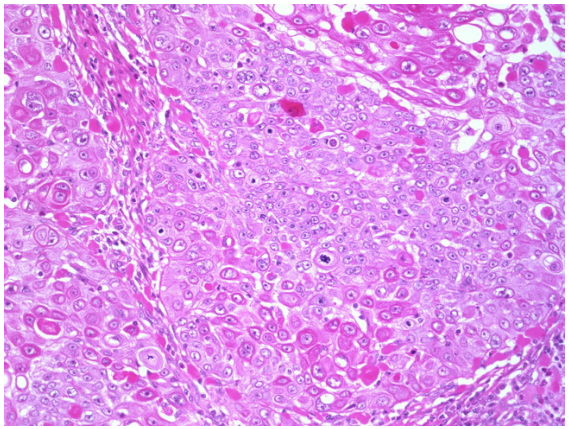
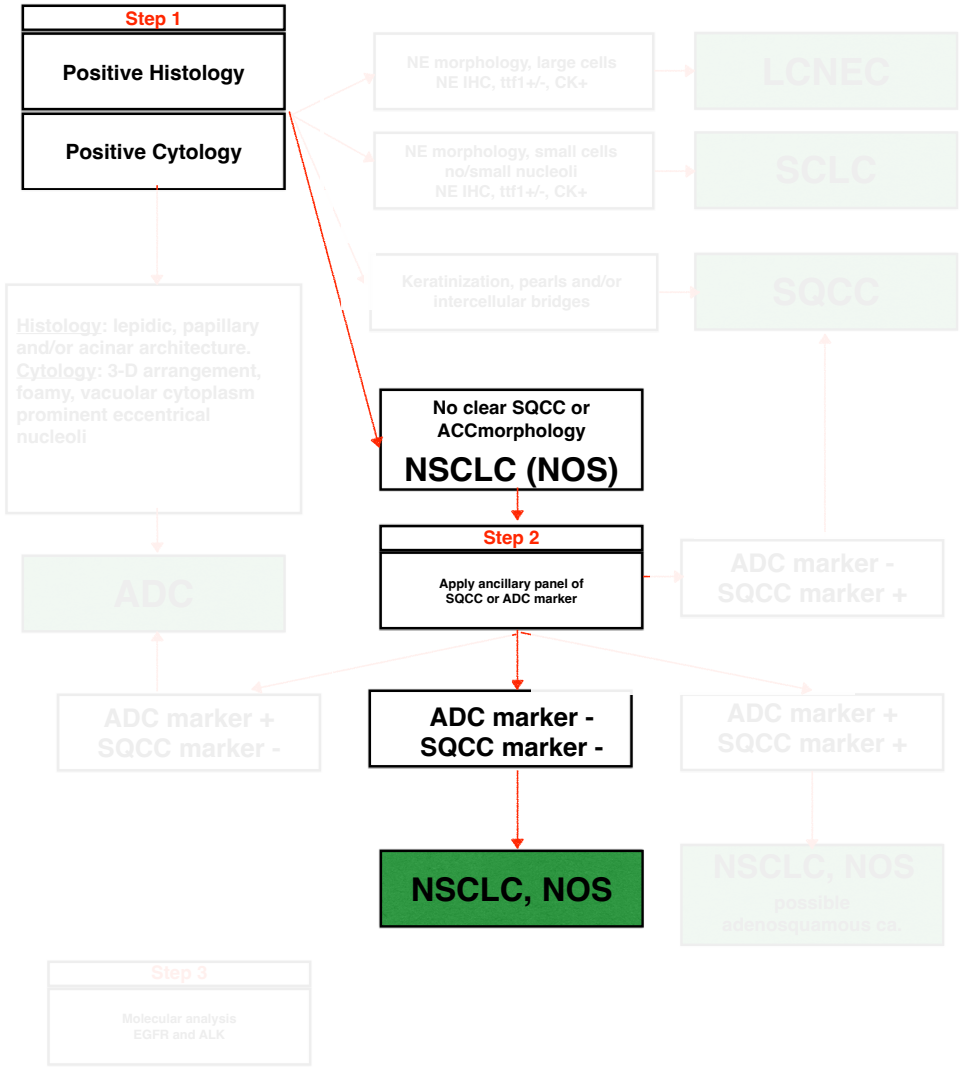
EGFR and ALK

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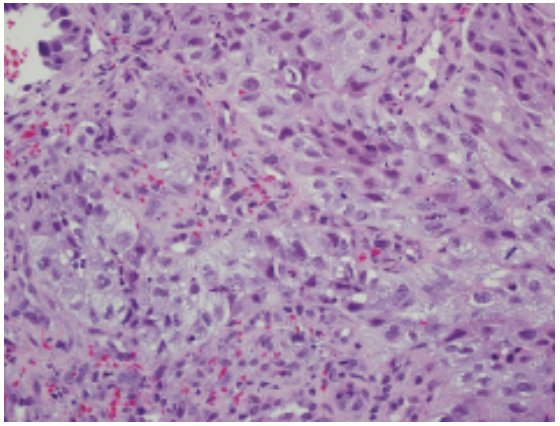
SQCC or ADC marker
ADC marker -
SQCC marker +
ADC
ADC marker +
SQCC marker -
ADC marker -
SQCC marker -
ADC marker +
SQCC marker +
NSCLC, NOS
NSCLC, NOS
possible
adenosquamous ca.
Step 3
Molecular analysis
EGFR and ALK

Ttf1- P63-



CK7

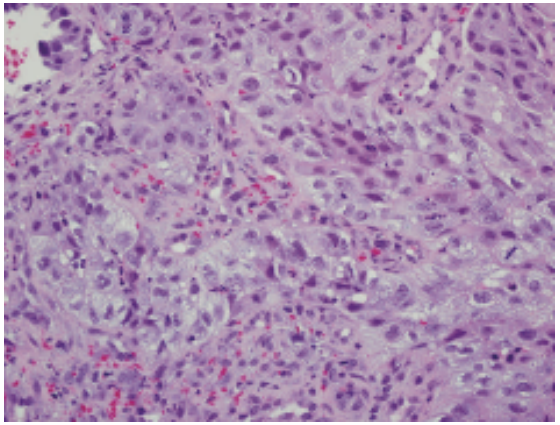
ttf1

Napsin

Adenocarcinoma (+neuroendocrine)
Approx. 80%

CK5/6

P63



CK7 50%

ttf1

Napsin

CK5/6

P63

Squamous carcinoma

Diagnosis of primary lung tumor

Lung1
CK7
Ttf1
PAX8
CK5(/6)
P63 (P40)

Suggestion

Lung2
PAN CK (AE1/AE3)
CK7
Ttf1
PAX8
CK5(/6)
P63 (P40)
Synaptofycin
ChromograninA
CD56
Ki67

Problems:

Adenocarcinoma can be P63+

The P63 family

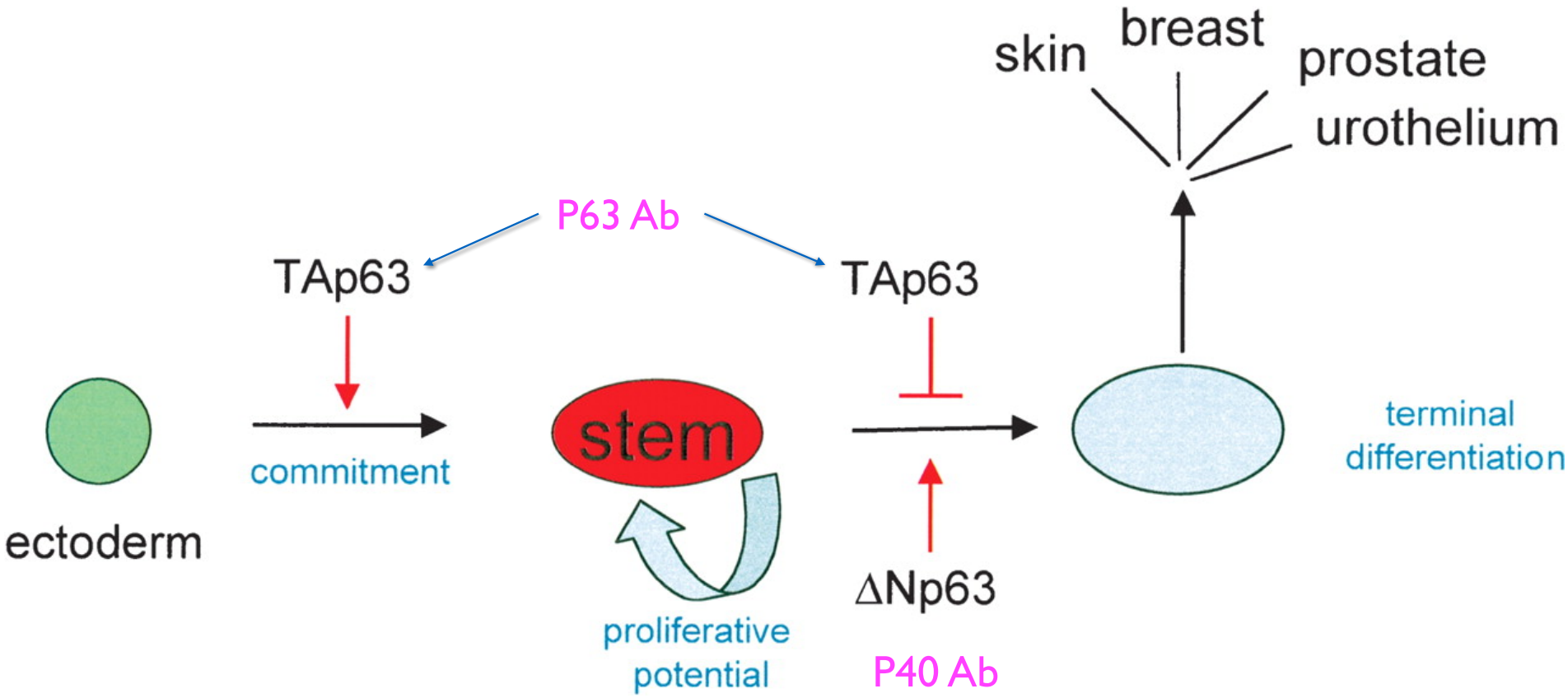


Table 8-1. Studies Comparing p40 Against p63 for Squamous Cell Carcinoma (SQCC)

Study	Total, n	SQCC, n	p40			p63		
			Clone	Sensitivity, %	Specificity, %	Clone	Sensitivity, %	Specificity, %
Bishop et al 2012	470	81	5-17	100	98	4A4	100	60
Nonaka 2012	200	50	p40	100	100	4A4	100	82
Pelosi et al 2013	141	27	Poly	100	97	4A4	100	78
Ao et al 2014	154	77	Poly	81	90	4A4	94	80
Koh et al 2014	184	59	Poly	93	98	7JUL	80	98
Tatsumori et al 2014	580	158	5-17	97	97	4A4	97	73
Kadota et al 2015	469	449	5-17	100	85	4A4	100	60
Tran et al 2016	557	167	BC28	94	96	4A4	95	87
Micke et al 2016	656	192	BC28	97	98	4A4	97	74
Affandi et al 2018	70	35	BC28	77	100	DAK-p63	86	63
Kriegsmann et al 2019	1244	569	BC28	94	97	4A4	94	84

Problems:

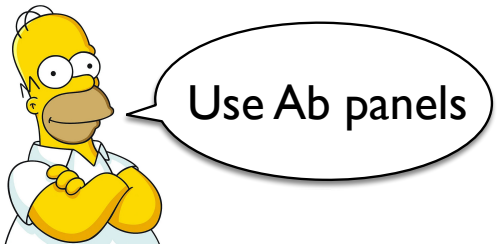
Differential diagnosis between primary and metastatic carcinoma

Other (adeno) carcinomas are positive for ttf1

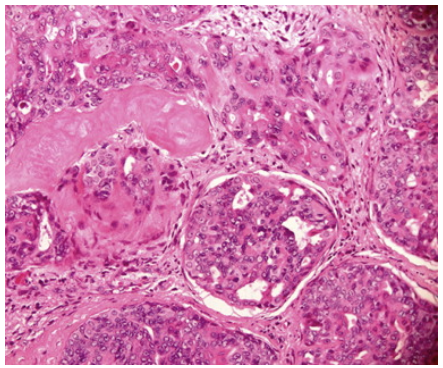
Table 7-1. Results of TTF1 Expression in Tumors from Non-Lung Primary Sites Including Female Genital Tract, Breast, Colon, and Stomach in Some Published Studies[a]

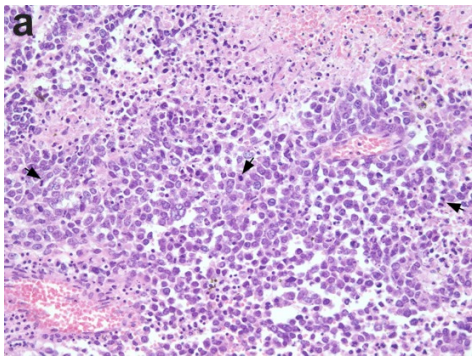
Primary carcinoma	8G7G3/1		SPT24	
	n	Positive, n (%)	n	Positive, n (%)
Ovarian carcinoma	615	22 (3.6%)	161	16 (9.9%)
Endometrial adenocarcinoma	215	17 (7.9%)	68	19 (27.9%)
Uterine cervical adenocarcinoma	92	3 (3.3%)	39	6 (15.4%)
Uterine cervical squamous carcinoma	7	0 (0%)		
Breast carcinoma	297	4 (1.5%)	580	13 (2.4%)
Colon adenocarcinoma	594	11 (1.8%)	258	15 (5.8%)
Gastric adenocarcinoma	170	3 (1.8%)	110	1 (0.9%)

[a] Data for clones 8G7G3/1 and SPT24 are modified based on data from Ordonez 2012b.



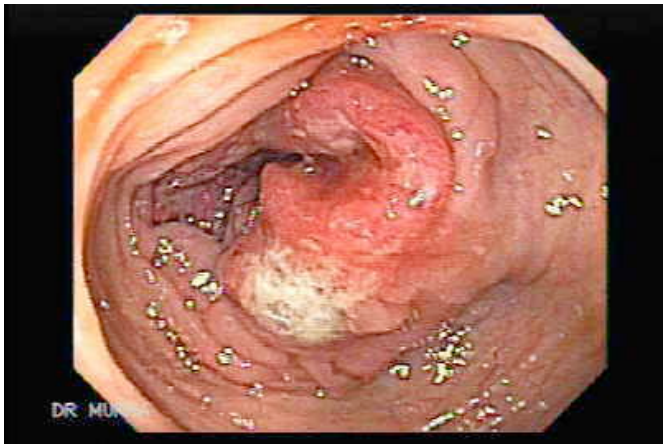
Diagnosis of metastasis to the lung



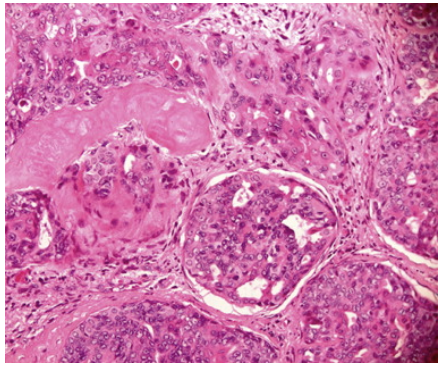


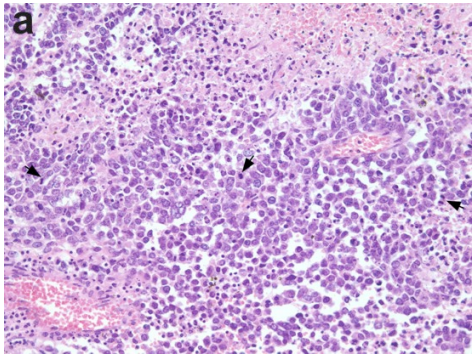
AE1/AE3 ←
CK7
ttf1
CK20 ←
cdx2 ←
SATB2 ←
NKX3.1
CK5/6
P63
CD10
PAX8
WT1
GATA3

Colon



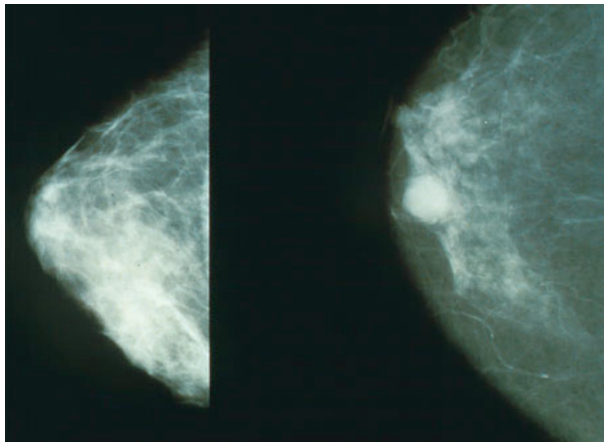
Diagnosis of metastasis to the lung



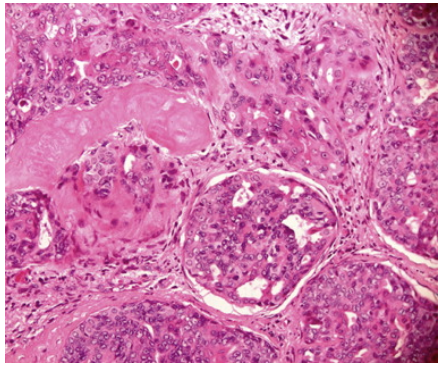


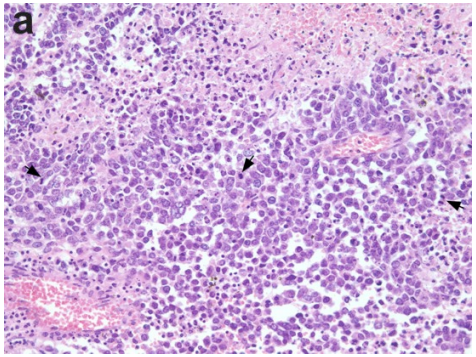
AE1/AE3 ←
CK7 ←
ttf1
CK20
cdx2
SATB2
NKX3.1
CK5/6
P63
CD10
PAX8
WT1
GATA3 ←

Mamma



Diagnosis of metastasis to the lung

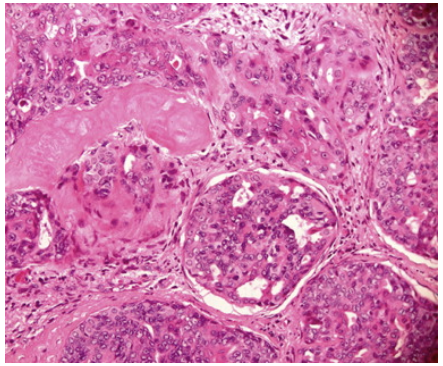


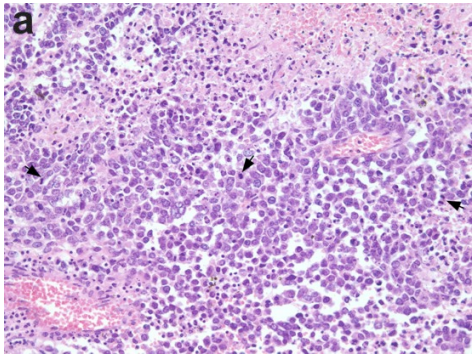


AE1/AE3 ←
CK7 ←
ttf1
CK20 ←
cdx2 ←
SATB2 ←
NKX3.1
CK5/6
P63
CD10
PAX8
WT1
GATA3

Upper GI

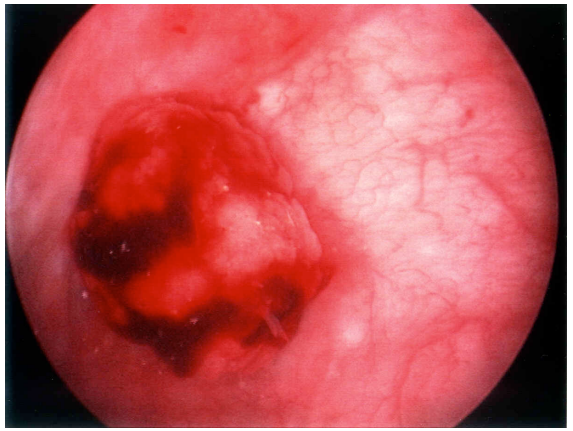
Diagnosis of metastasis to the lung



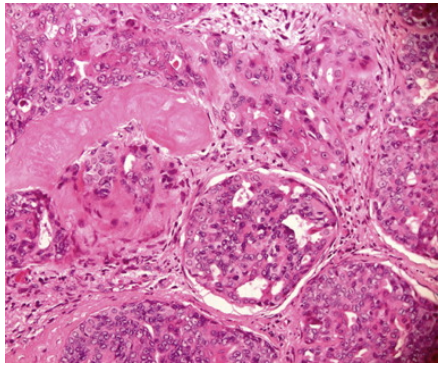


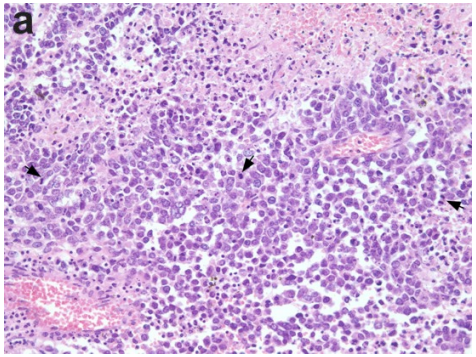
AE1/AE3 ←
CK7 ←
ttf1
CK20 ←
cdx2
SATB2
NKX3.1
CK5/6 ←
P63 ←
CD10
PAX8
WT1
GATA3 ←

Urothelial carcinoma



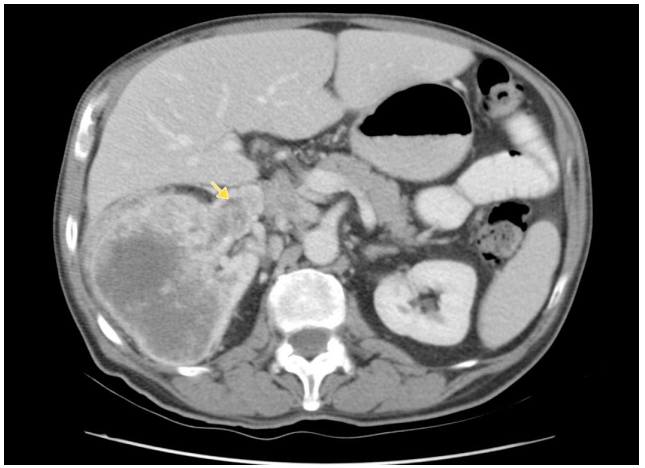
Diagnosis of metastasis to the lung



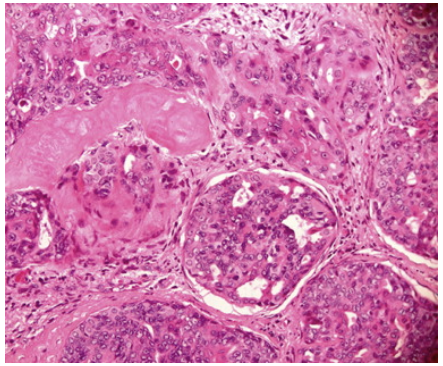


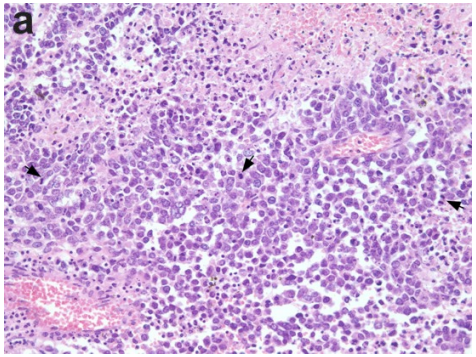
AE1/AE3 ←
CK7
ttf1
CK20
cdx2
SATB2
NKX3.1
CK5/6
P63
CD10 ←
PAX8 ←
WT1
GATA3

Renal cell carcinoma



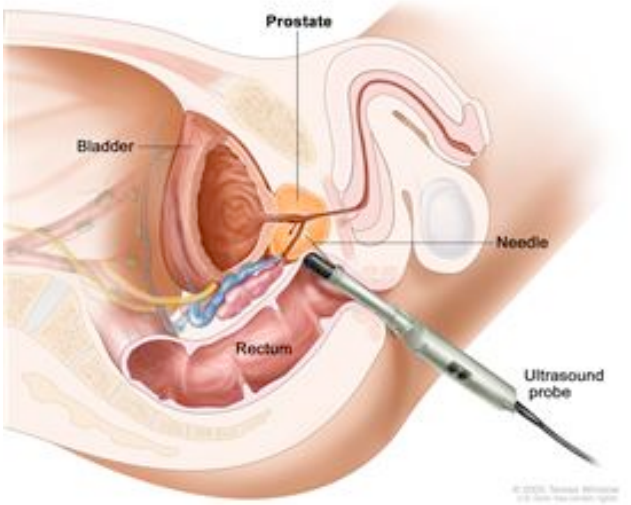
Diagnosis of metastasis to the lung



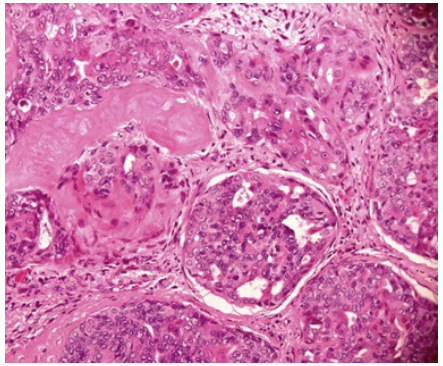


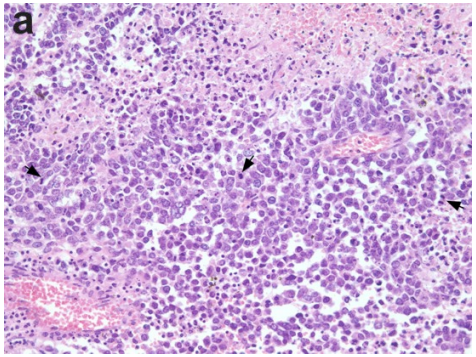
AE1/AE3 ←
CK7
ttf1
CK20
cdx2
SATB2
NKX3.1 ←
CK5/6
P63
CD10
PAX8
WT1
GATA3

Prostate



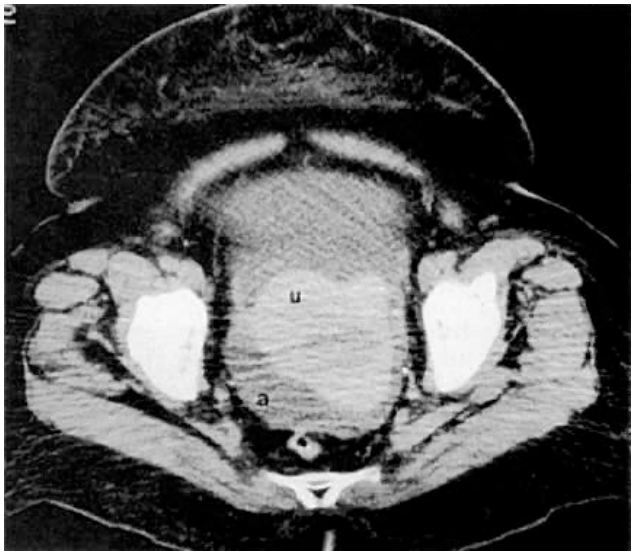
Diagnosis of metastasis to the lung



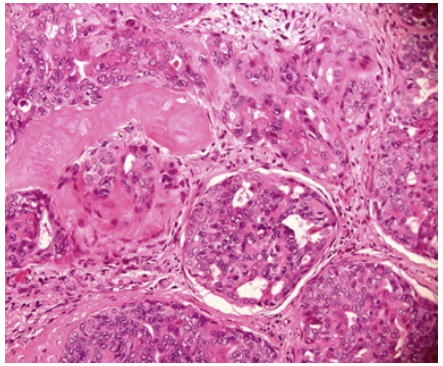


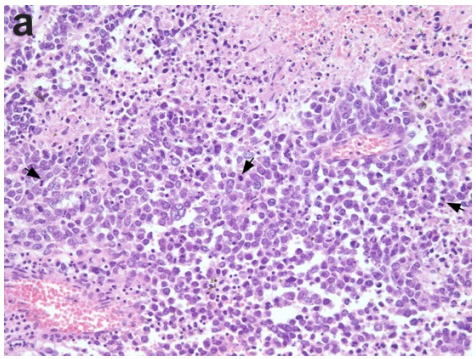
AE1/AE3 ←
CK7 ←
ttf1
CK20
cdx2
SATB2
NKX3.1
CK5/6
P63
CD10
PAX8 ←
WT1 ←
GATA3

Endometrial cancer



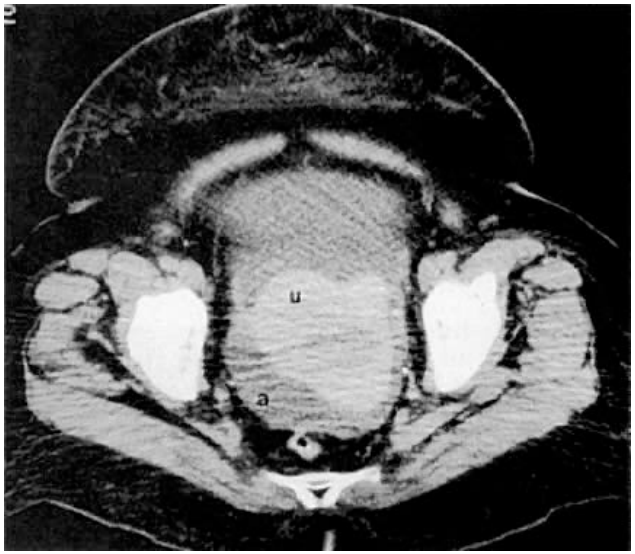
Diagnosis of metastasis to the lung



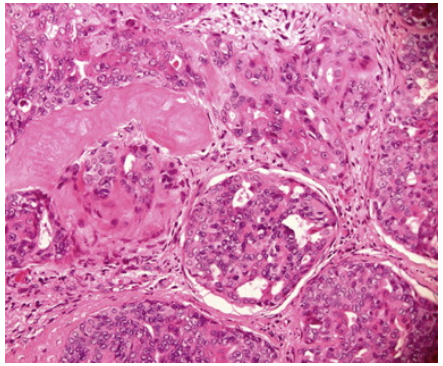


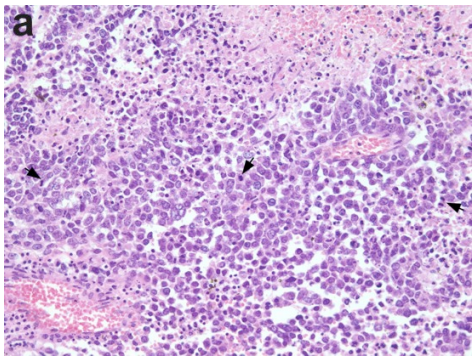
AE1/AE3 ←
CK7 ←
ttf1
CK20
cdx2
SATB2
NKX3.1
CK5/6
P63
CD10
PAX8 ←
WT1 ←
GATA3

Ovarian cancer



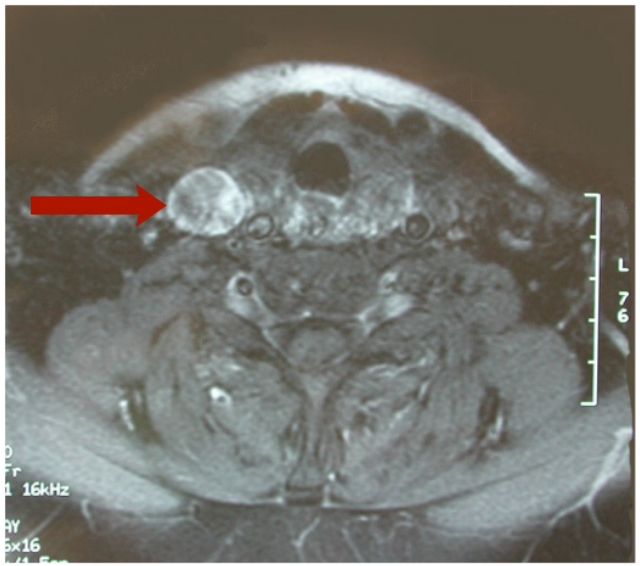
Diagnosis of metastasis to the lung



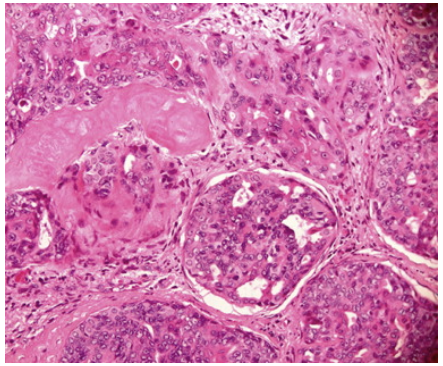


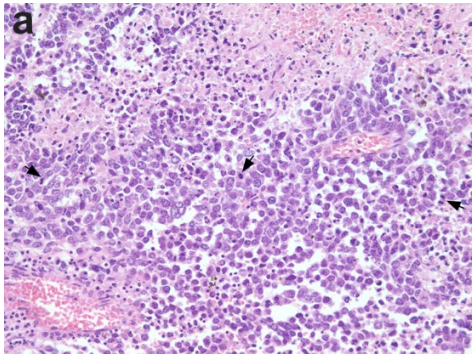
AE1/AE3 ←
CK7 ←
ttf1 ←
CK20
cdx2
SATB2
NKX3.1
CK5/6
P63
CD10
PAX8 ←
WT1
GATA3

Thyroid cancer



Diagnosis of metastasis to the lung





Calretinin
WT1
D2-40
CK7
Vim
CK5/6
(EpCam)

Mesothelioma

Diagnosis of metastasis to the lung

NordiQC

Adeno - male

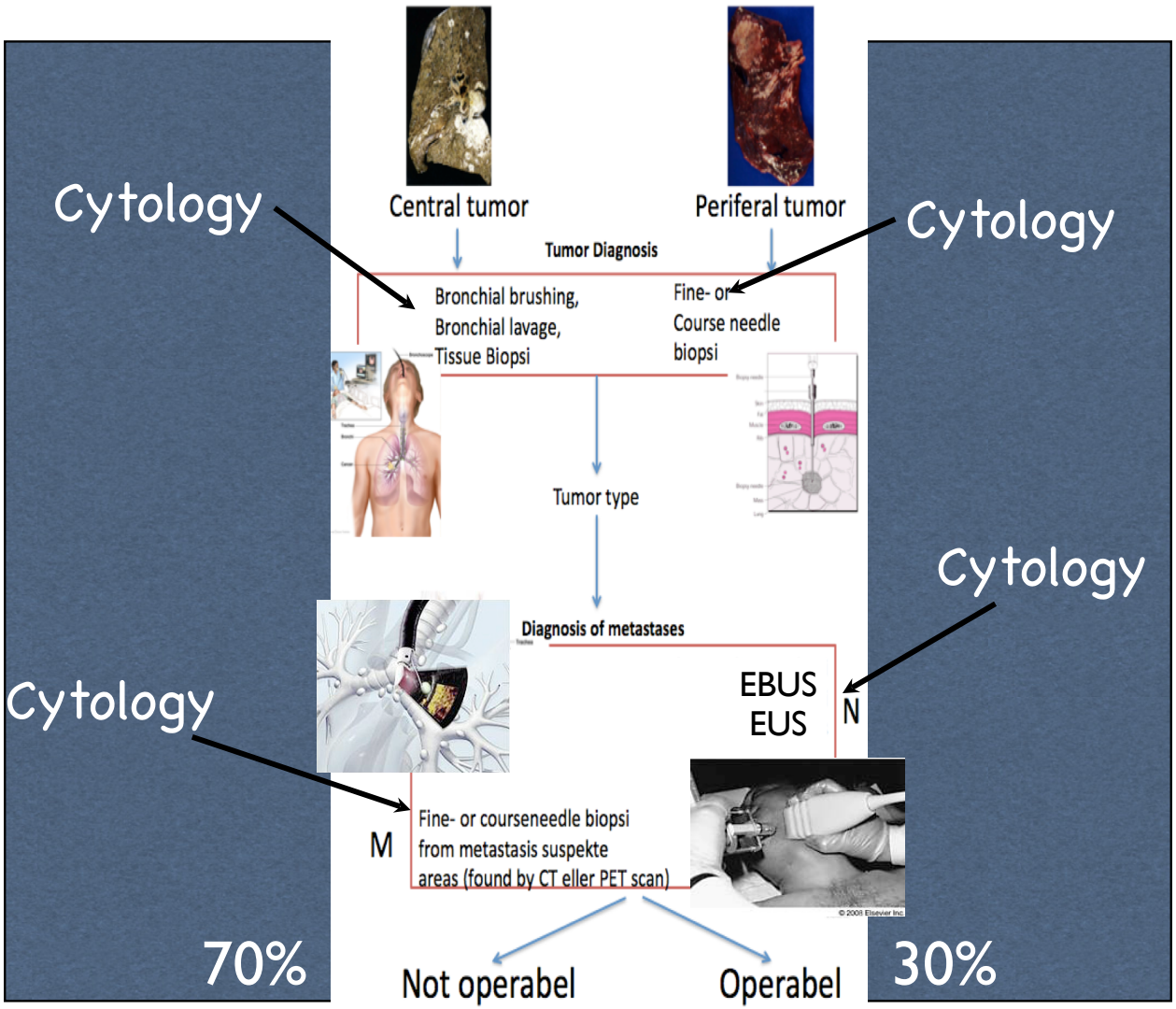
CK7
CK20
CDX2
Ttf1
PAX8
NKX3.1

Suggestion

Adeno - female

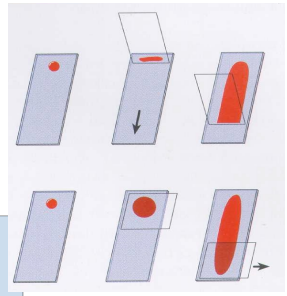
CK7
CK20
CDX2
Ttf1
PAX8
GATA3
WT1
ER

The MultiDisciplinary Teamconference
MDT


Cytology
Central tumor
Periferal tumor
Cytology
Tumor Diagnosis
Bronchial brushing,
Bronchial lavage,
Tissue Biopsi
Fine- or
Course needle
biopsi
Tumor type
Cytology
Diagnosis of metastases
Cytology
EBUS
EUS
N
M
Fine- or courseneedle biopsi
from metastasis suspekte
areas (found by CT eller PET scan)
70%
Not operabel
Operabel
30%

Patoanatomical specimen

Cytology



Histology

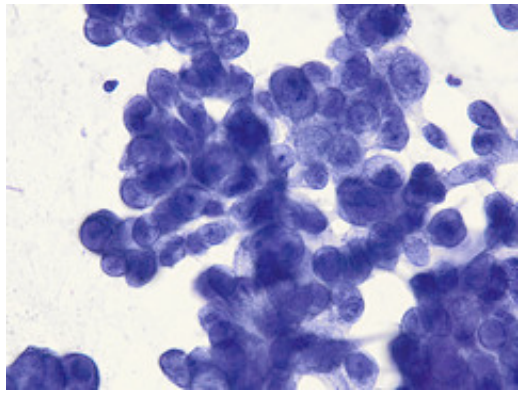
Fixation
Dehydration
Parafinembedding
Microtomy

Præparation

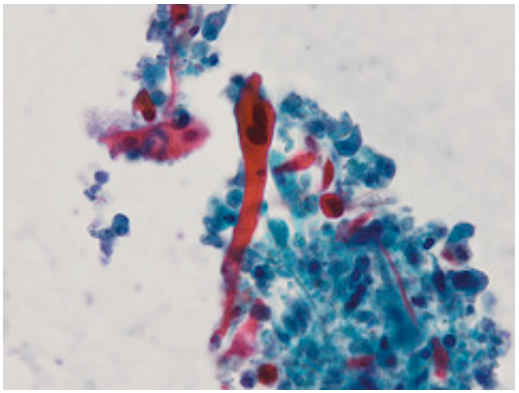
Smear preparation

Visualization

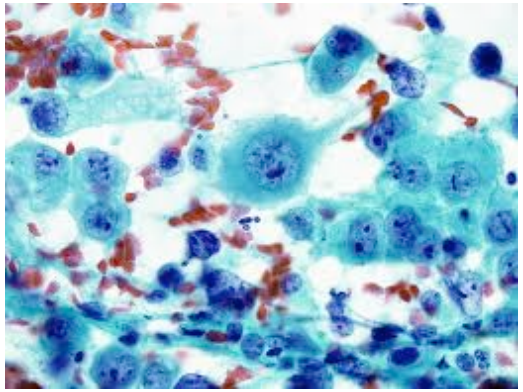
(Staining)



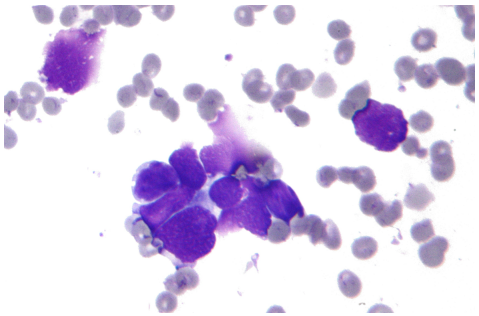
Adenocarcinoma



Squamous carcinoma



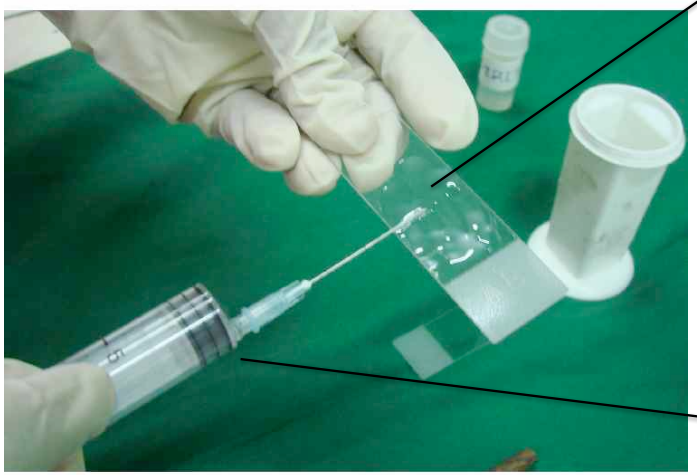
Large cell
neuroendocrine carc.

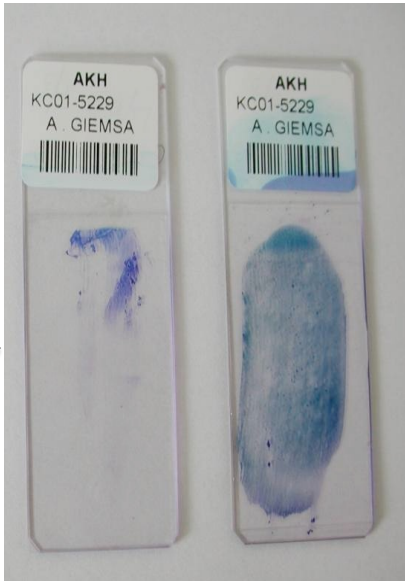


Small cell carcinoma

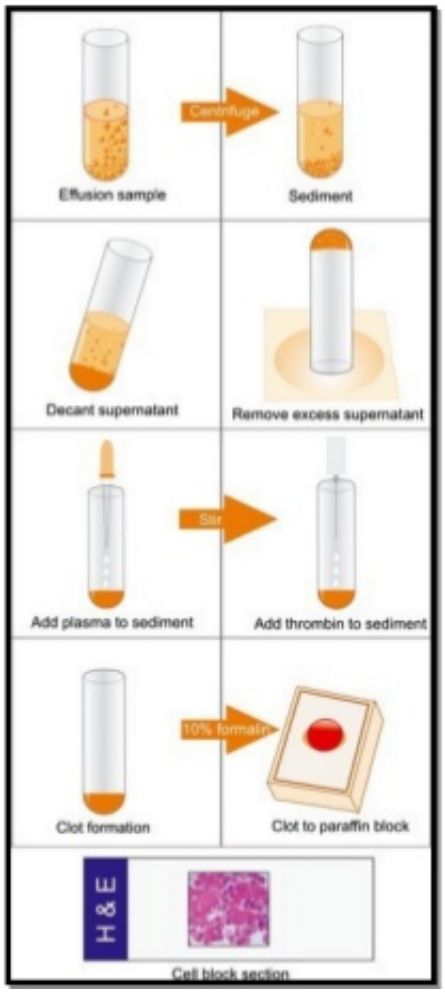
Non Small Cell Lung Carcinoma (NSCLC)

Immuncytology



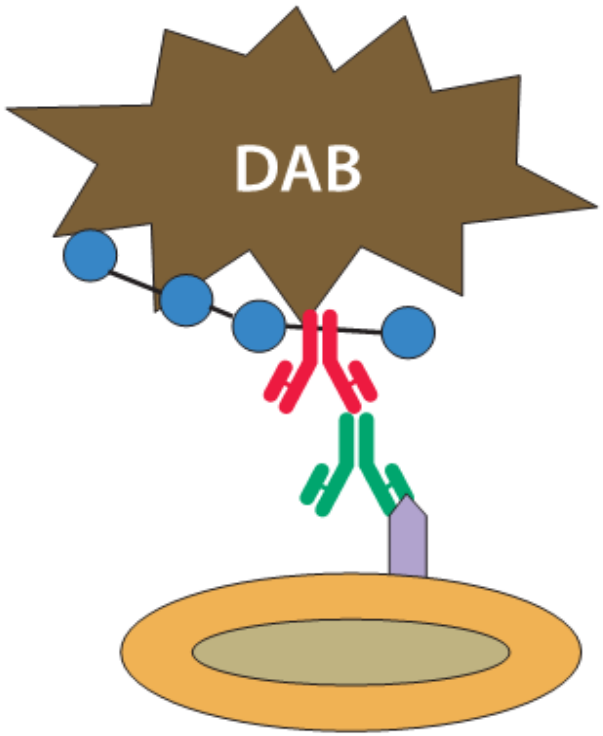


Smear



Cellblock

Immuncytology



Kromogen (farvestof)

Visualiseringssystem (enzymer)

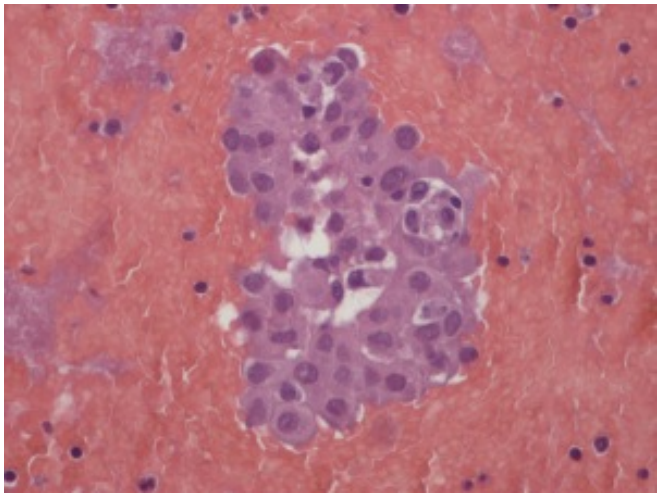
Sekundært antistof

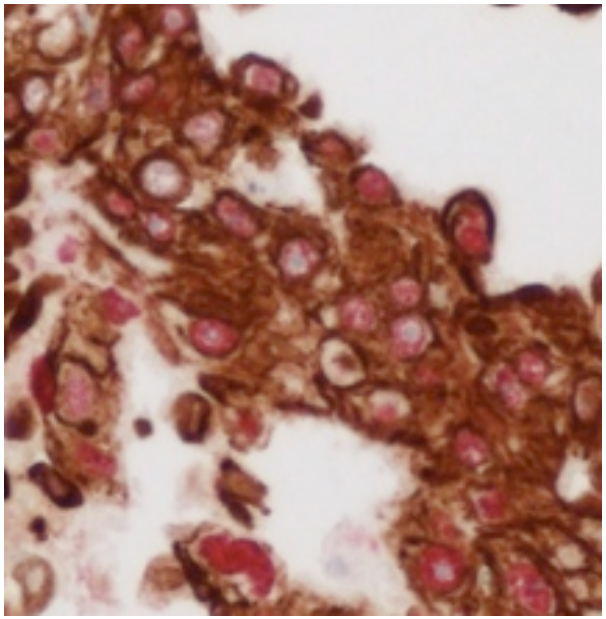
Primært antistof

Antigen

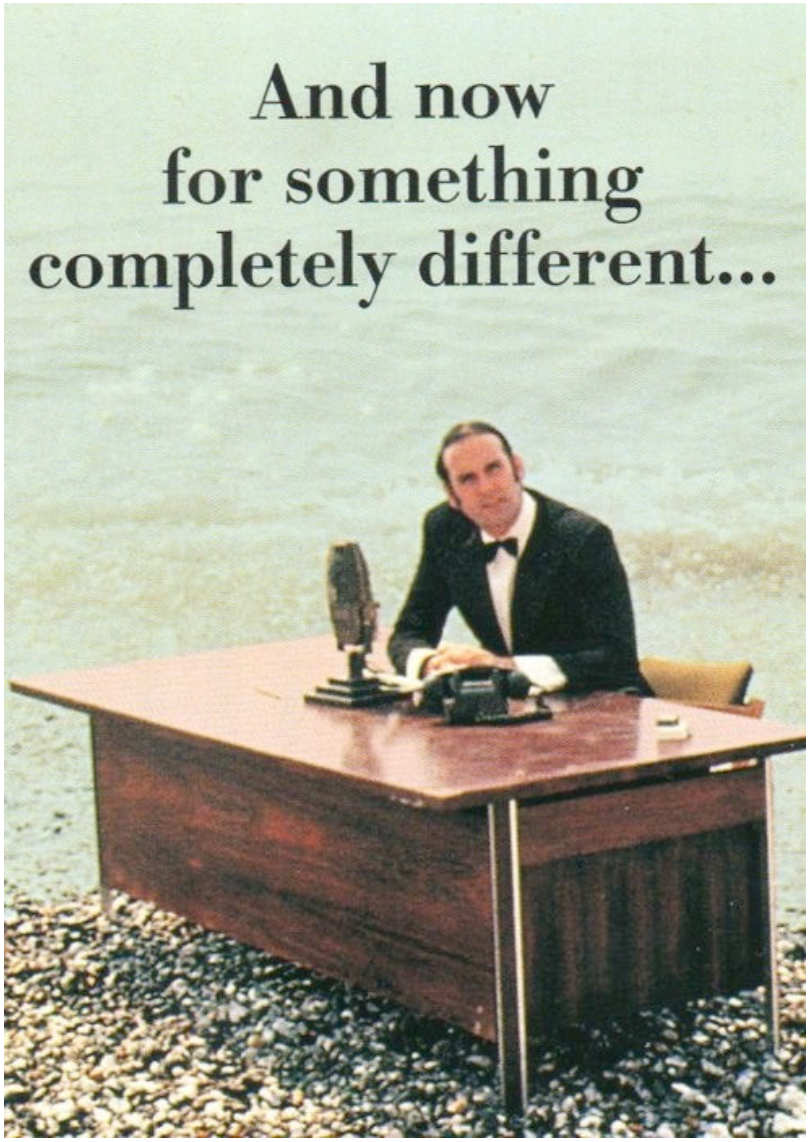
Cellens cytoplasma

Cellekerne



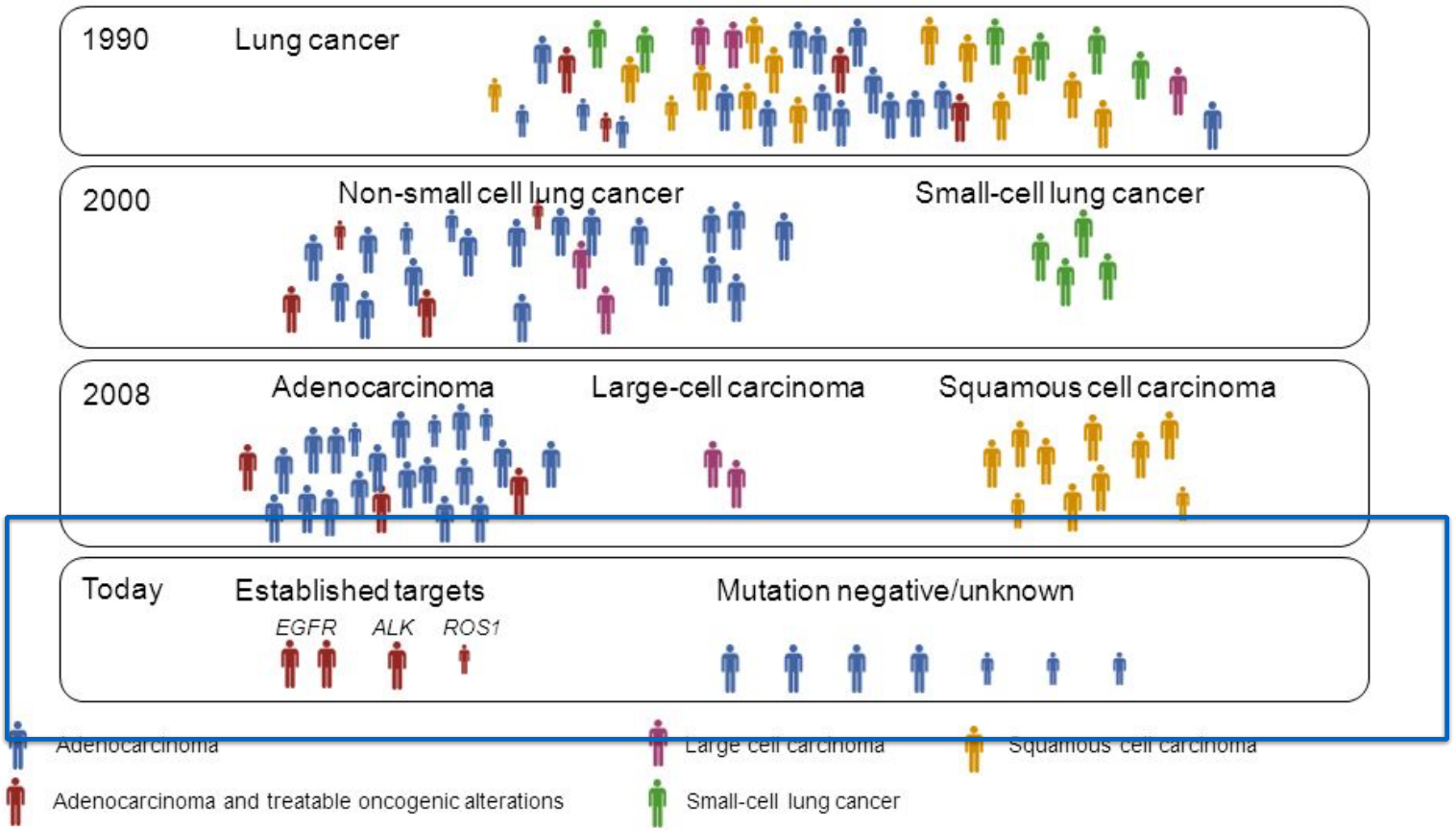


ttf1-CK7

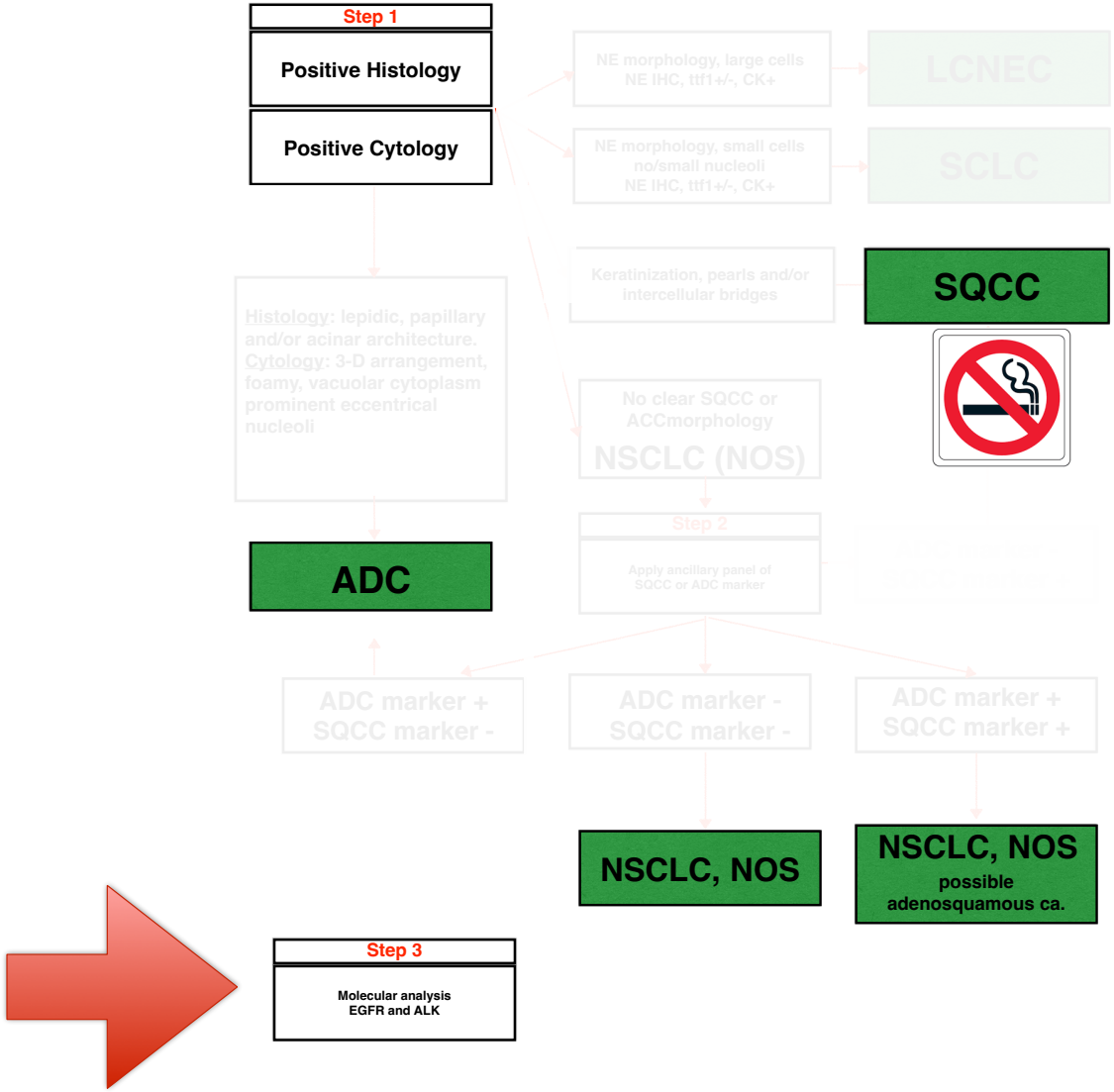


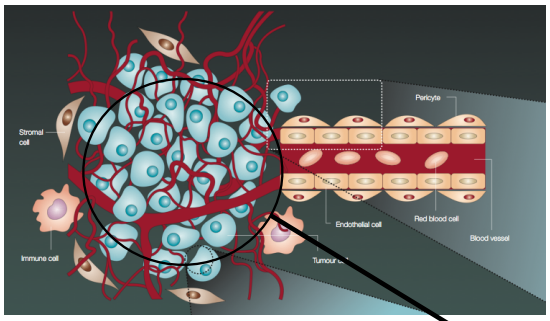
NordIQC

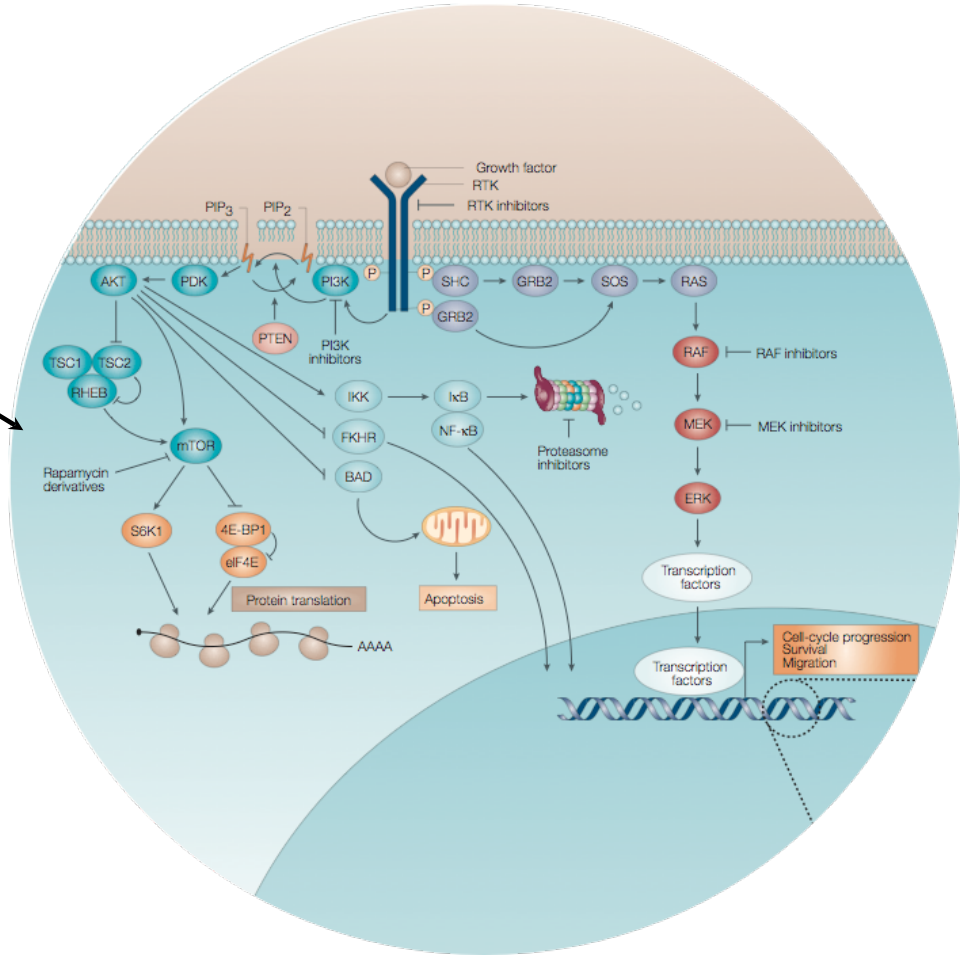
Patient selection in lung cancer: Evolution over time



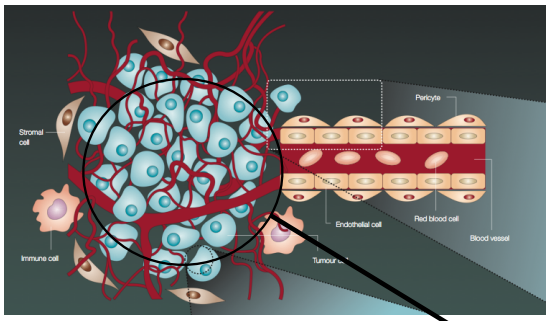
Adapted from Reck M, et al. Lancet 2013;382:709–19

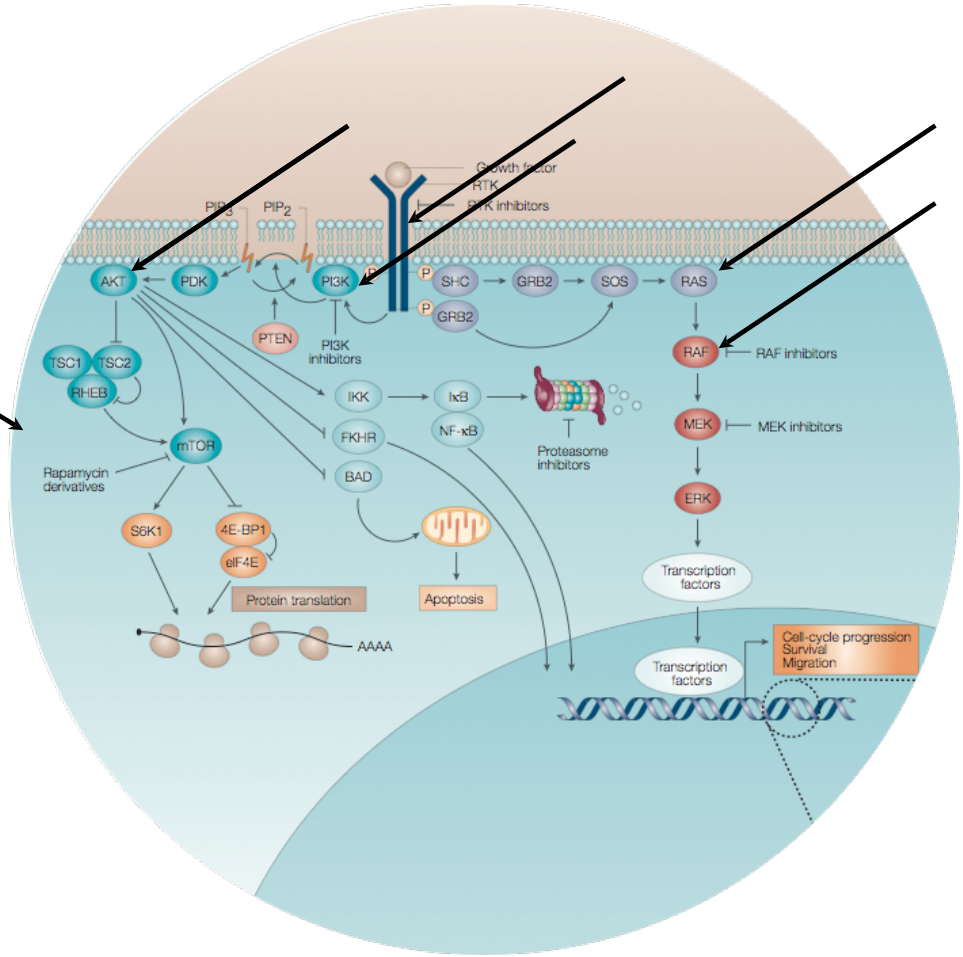

Step 1
Positive Histology
Positive Cytology
NE morphology, large cells
NE IHC, ttf1+/-, CK+
LCNEC
NE morphology, small cells
no/small nucleoli
NE IHC, ttf1+/-, CK+
SCLC
Keratinization, pearls and/or
intercellular bridges
SQCC
Histology: lepidic, papillary
and/or acinar architecture.
Cytology: 3-D arrangement,
foamy, vacuolar cytoplasm
prominent eccentrical
nucleoli
No clear SQCC or
ACCmorphology
NSCLC (NOS)
Step 2
Apply ancillary panel of
SQCC or ADC marker
ADC
ADC marker +
SQCC marker -
ADC marker -
SQCC marker -
ADC marker +
SQCC marker +
NSCLC, NOS
NSCLC, NOS
possible
adenosquamous ca.
Step 3
Molecular analysis
EGFR and ALK





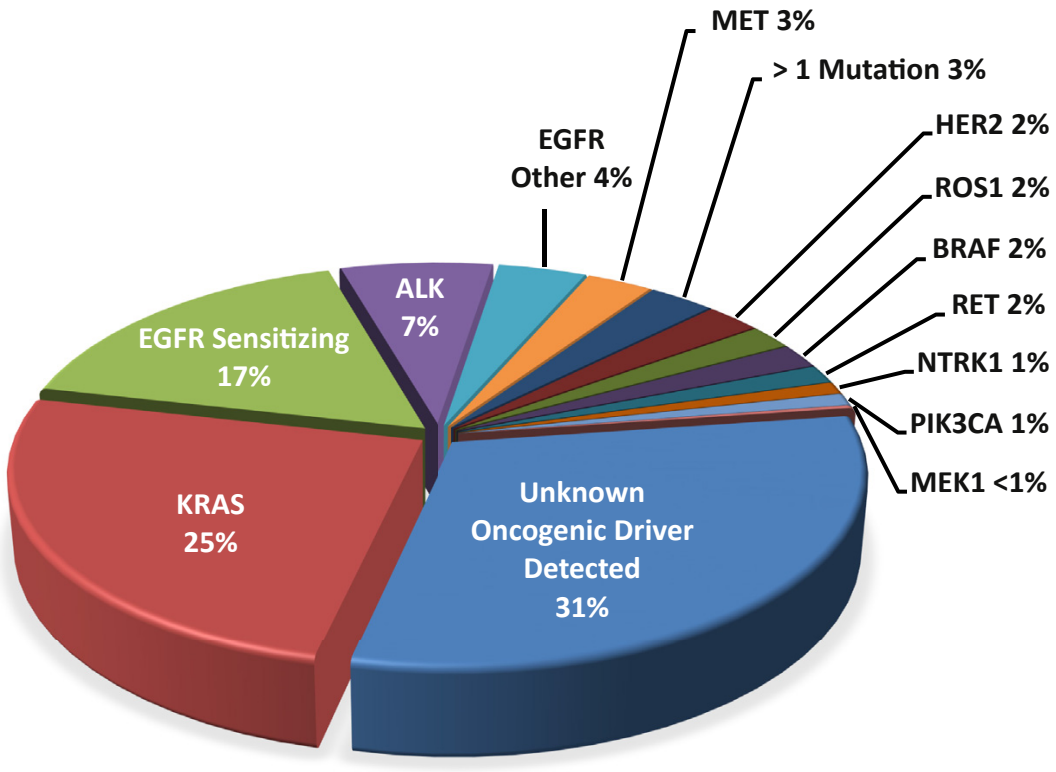
Pathways of cancer


Pericyte
Stromal cell
Endothelial cell
Red blood cell
Blood vessel
Immune cell


Growth factor
RTK
RTK inhibitors
PIP3
PIP2
AKT
PDK
PI3K
P
SHC
GRB2
SOS
RAS
GRB2
PTEN
PI3K inhibitors
RAF
RAF inhibitors
TSC1
TSC2
RHEB
IKK
IκB
NF-κB
Proteasome inhibitors
MEK
MEK inhibitors
mTOR
FKHR
BAD
Rapamycin derivatives
ERK
S6K1
4E-BP1
eIF4E
Protein translation
Apoptosis
Transcription factors
AAAA
Transcription factors
Cell-cycle progression
Survival
Migration

oncogenes

Driver mutations
Lung Adenocarcinoma

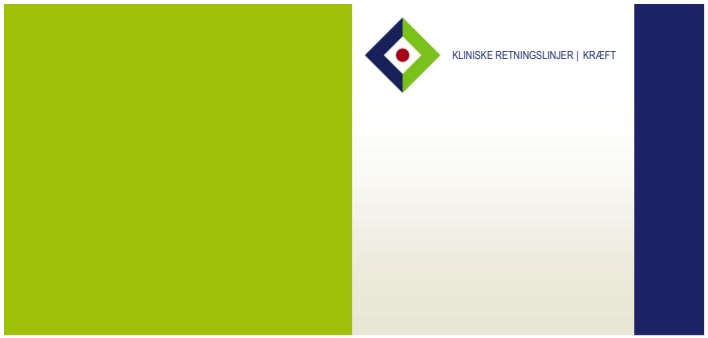


STATE OF THE ART: CONCISE REVIEW

Scientific Advances in Lung Cancer 2015

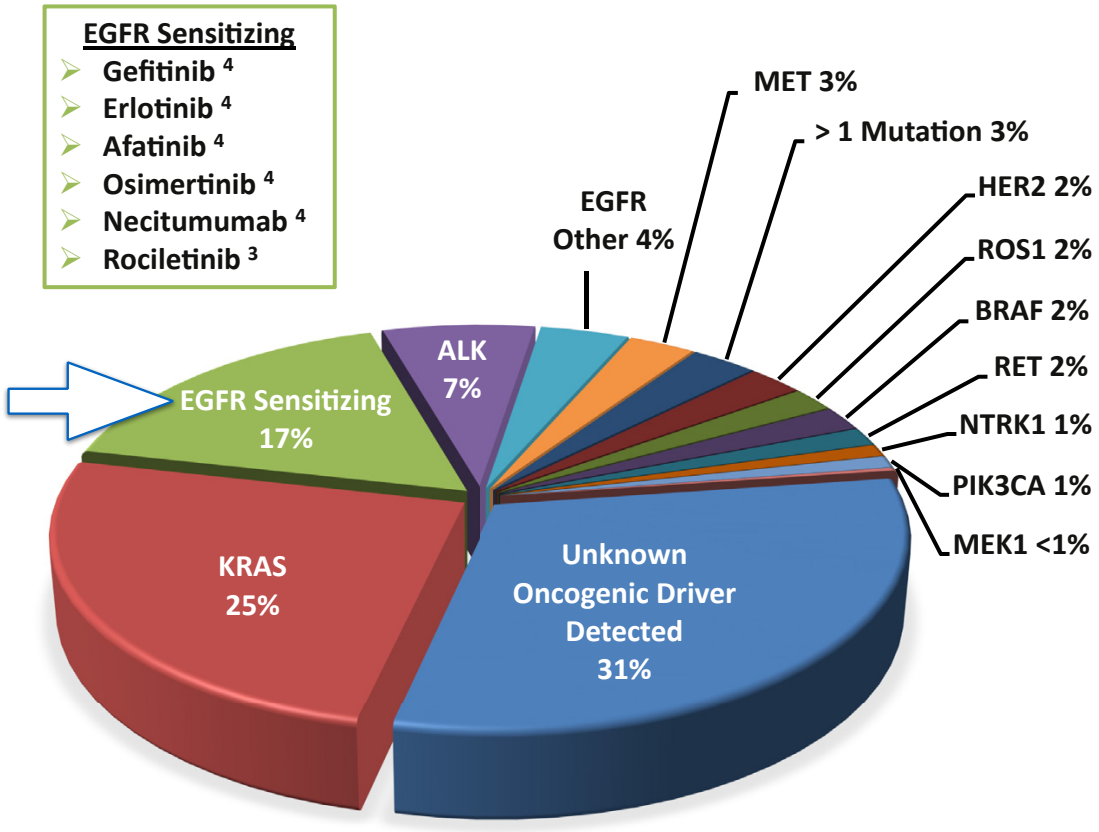
Journal of Thoracic Oncology *Vol. 11 No. 5: 613-638*

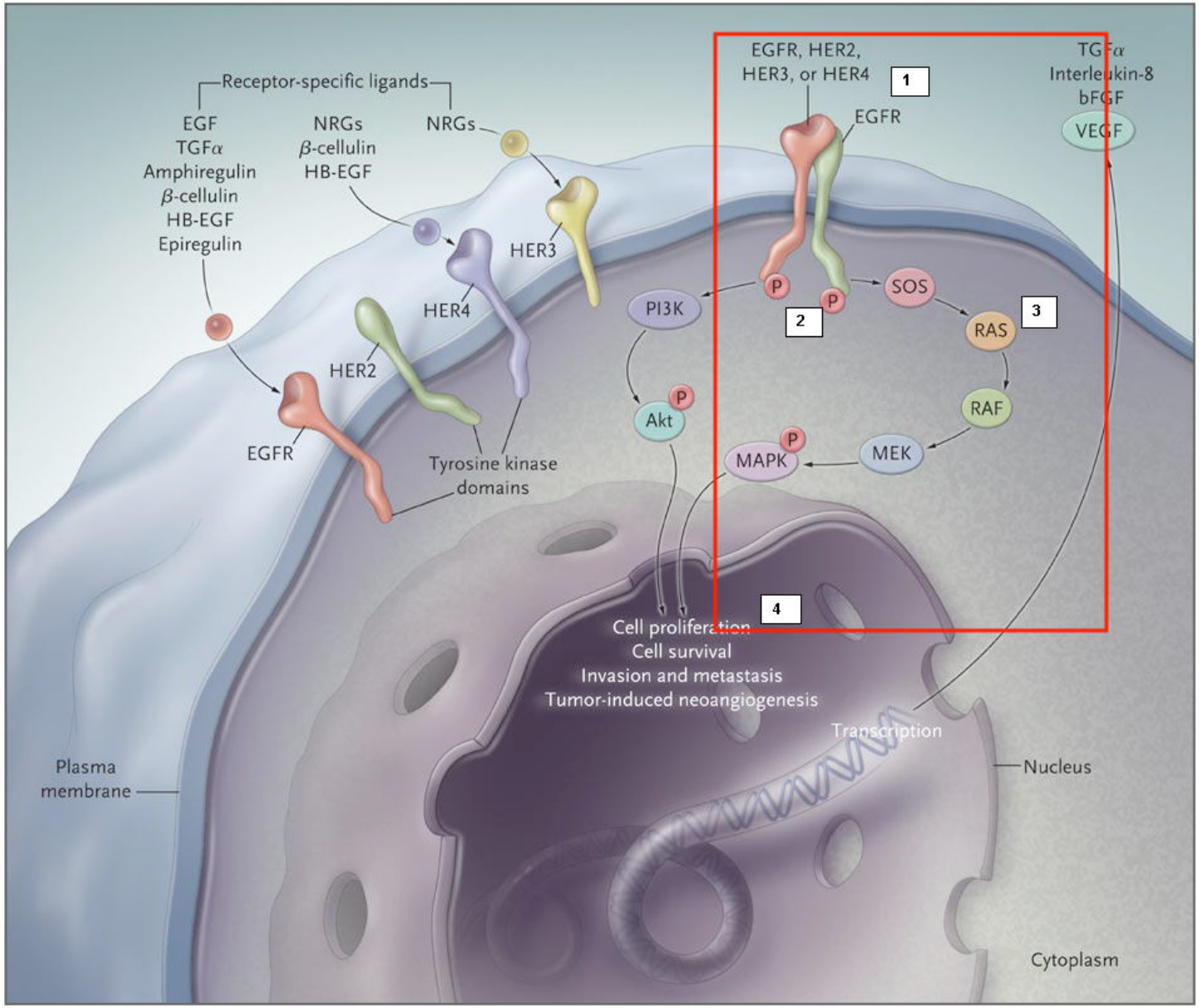
Danish Lung Cancer Group (DLCG)

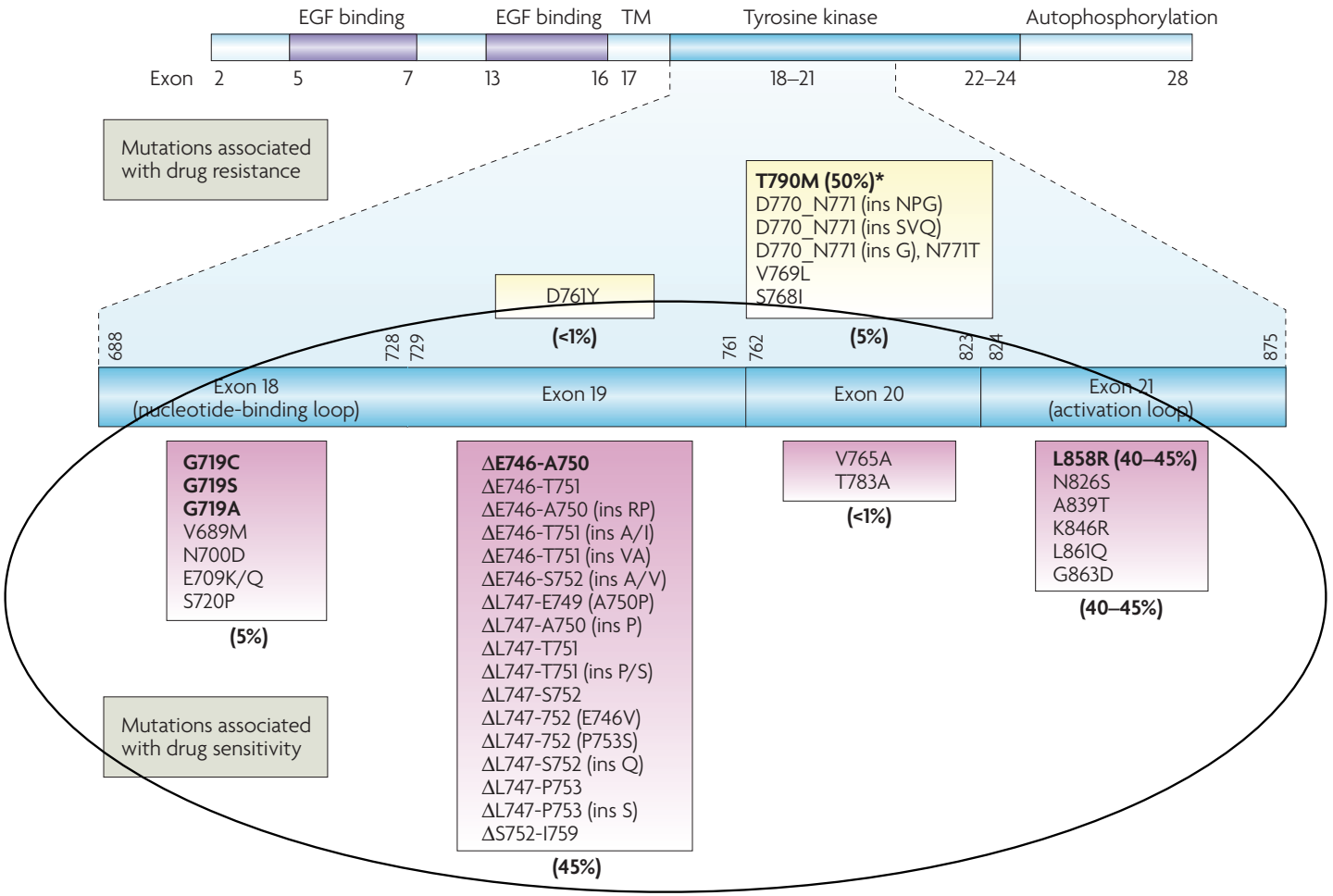


Lungecancer – Patologi

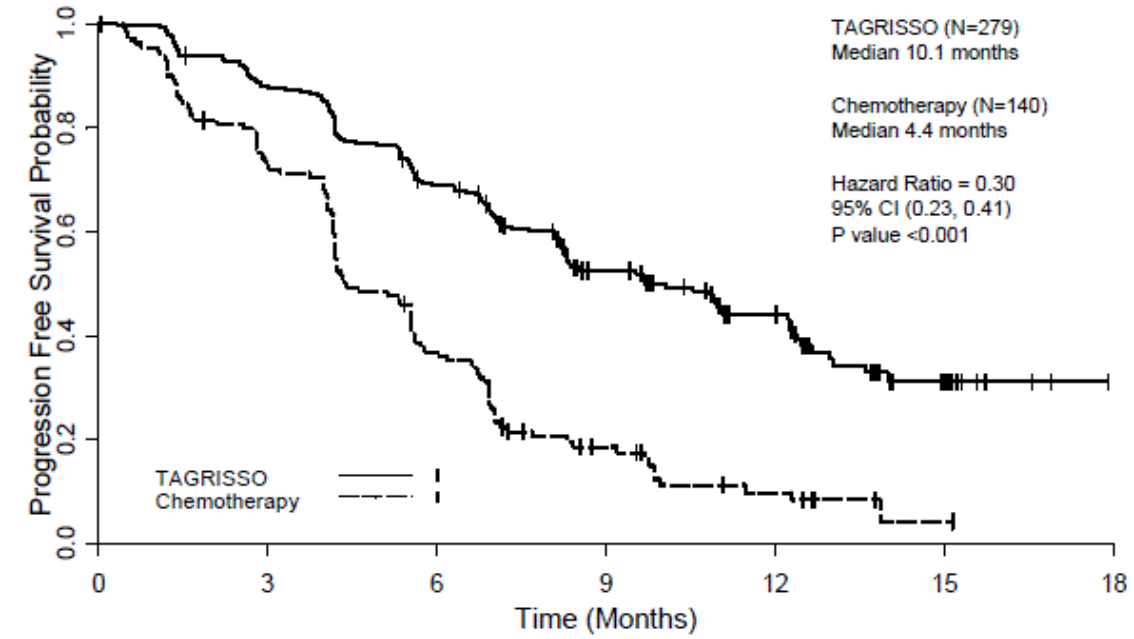
46. **Reflextest af de obligatoriske markører bør foretages ved den primære diagnostik af nedenstående grupper. (A)**
    - **EGFR, ALK, ROS1: adenokarcinomer + ikke-småcellede karcinomer, hvor typen ikke sikkert kan afgøres**
    - **PD-L1: alle ikke-småcellede karcinomer**


EGFR Sensitizing
Gefitinib 4
Erlotinib 4
Afatinib 4
Osimertinib 4
Necitumumab 4
Rociletinib 3
EGFR Sensitizing 17%
ALK 7%
EGFR Other 4%
MET 3%
> 1 Mutation 3%
HER2 2%
ROS1 2%
BRAF 2%
RET 2%
NTRK1 1%
PIK3CA 1%
MEK1 <1%
KRAS 25%
Unknown Oncogenic Driver Detected 31%


Receptor-specific ligands
EGF
TGFα
Amphiregulin
β-cellulin
HB-EGF
Epiregulin
NRGs
β-cellulin
HB-EGF
NRGs
HER3
HER4
HER2
EGFR
Tyrosine kinase domains
EGFR, HER2, HER3, or HER4
1
EGFR
TGFα
Interleukin-8
bFGF
VEGF
P
P
2
PI3K
SOS
3
RAS
RAF
Akt
P
MAPK
P
MEK
4
Cell proliferation
Cell survival
Invasion and metastasis
Tumor-induced neoangiogenesis
Transcription
Nucleus
Plasma membrane
Cytoplasm



autoactivates EGFR



Number at risk

TAGRISSO	279	240	162	88	50	13	0
Chemotherapy	140	93	44	17	7	1	0

Tick marks represent censored observations

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Novel EGFR mutation-specific antibodies for lung adenocarcinoma: Highly specific but not sensitive detection of an E746_A750 deletion in exon 19 and an L858R mutation in exon 21 by immunohistochemistry

An Na Seo[a,b,1], Tae-In Park[b,1], Yan Jin[a,c], Ping-Li Sun[a,c], Hyojin Kim[a,c], Hyun Chang[d], Jin-Haeng Chung[a,c,*]

[a] Department of Pathology, Seoul National University Bundang Hospital, 300 Gumi-dong, Bundang-gu, Seongnam-si, Gyeonggi 463-707, Republic of Korea
[b] Department of Pathology, Kyungpook National University College of Medicine, 680 Gukchaebosang-ro, Jung-gu, Daegu 700-842, Republic of Korea
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[d] Department of Internal Medicine, Seoul National University Bundang Hospital, 300 Gumi-dong, Bundang-gu, Seongnam-si, Gyeonggi 463-707, Republic of Korea

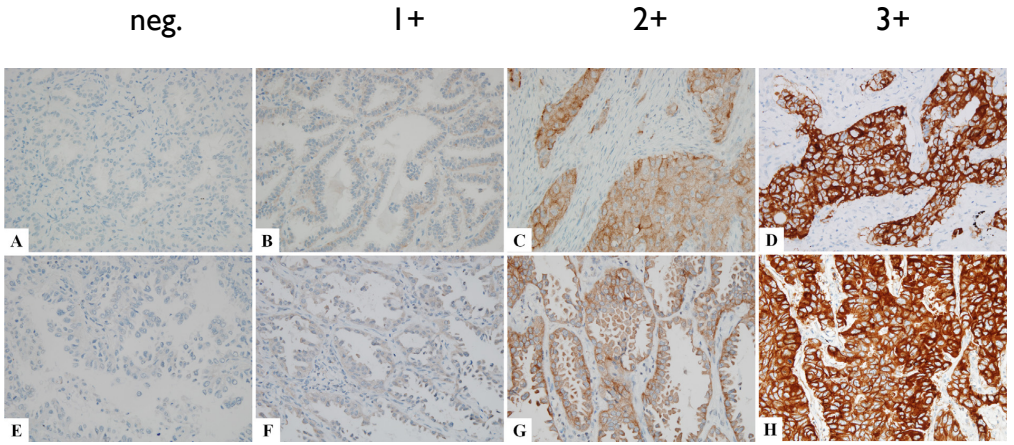
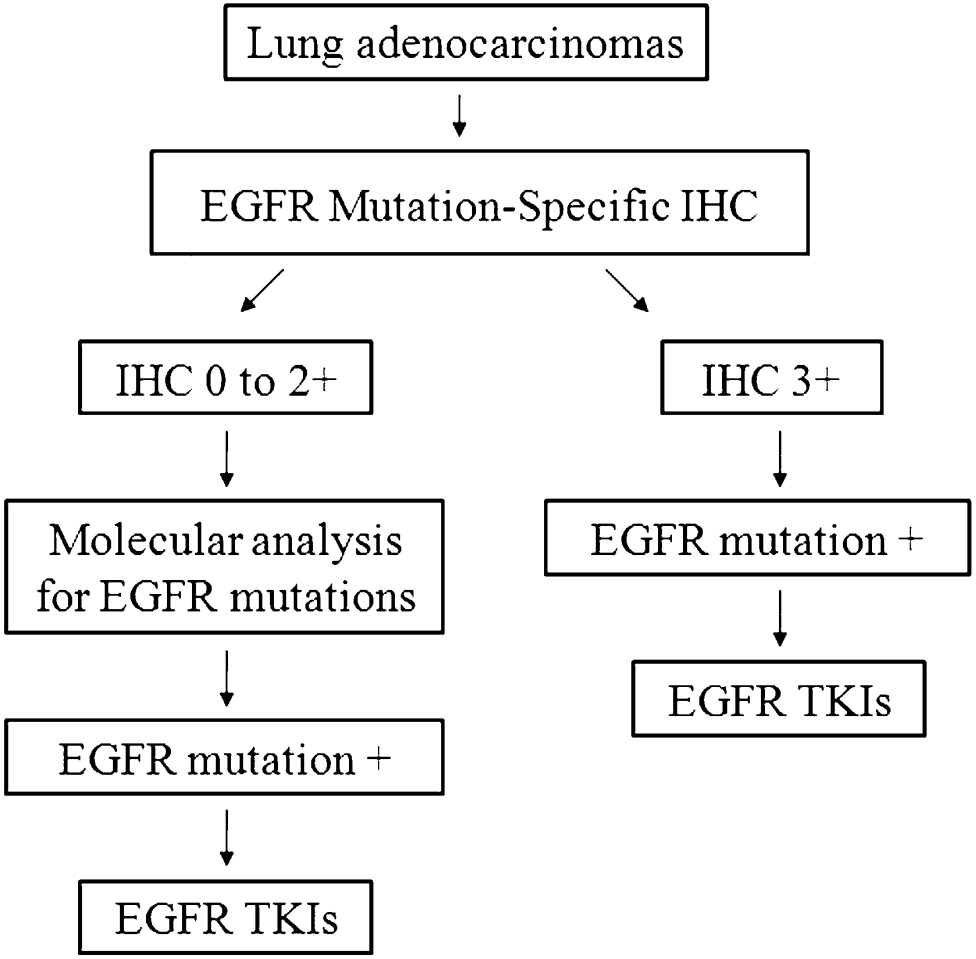


Table 2
Diagnostic power of mutation-specific antibodies comparing with *EGFR* mutational status.

Mutation-specific antibodies	*EGFR* mutations	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Anti-EGFR E746_A750 del	E746_A750 deletion				
	≥Score 1 as positive	94.1%	96.1%	80.0%	99.0%
	≥Score 2 as positive	70.6%	99.0%	92.3%	95.3%
	≥Score 3 as positive	29.4%	100.0%	100.0%	89.6%
	All deletions in exon 19				
	≥Score 1 as positive	54.8%	96.6%	85.0%	86.0%
	≥Score 2 as positive	40.3%	99.4%	96.2%	82.7%
	≥Score 3 as positive	16.1%	100.0%	100.0%	77.4%
Anti-EGFR L858R	L858R				
	≥Score 1 as positive	93.5%	50.0%	30.7%	97.0%
	≥Score 2 as positive	80.4%	89.7%	64.9%	95.1%
	≥Score 3 as positive	41.3%	100.0%	100.0%	87.8%

Abbreviations: PPV, positive predictive value; NPV, negative predictive value.

Algorithm



Lung Cancer

Novel EGFR mutation-specific antibodies for lung adenocarcinoma: Highly specific but not sensitive detection of an E746_A750 deletion in exon 19 and an L858R mutation in exon 21 by immunohistochemistry

DNA(template)

PCR

Analysis

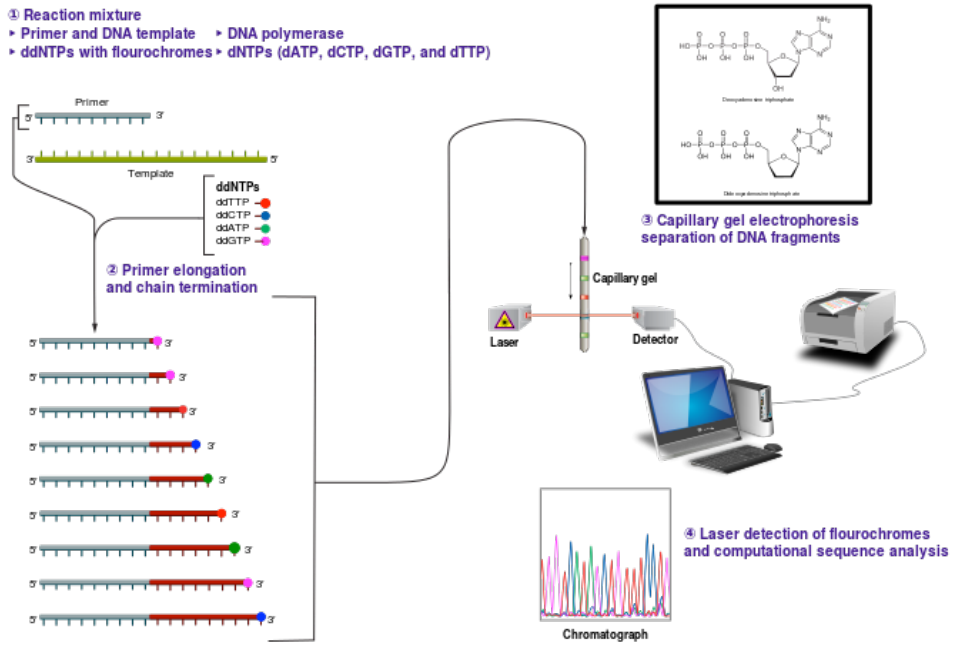
DNA-purification

Tissue section

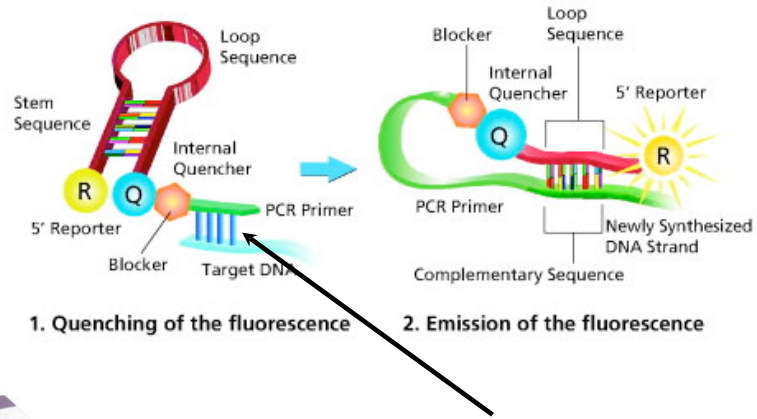
NordIQC

Sequencing

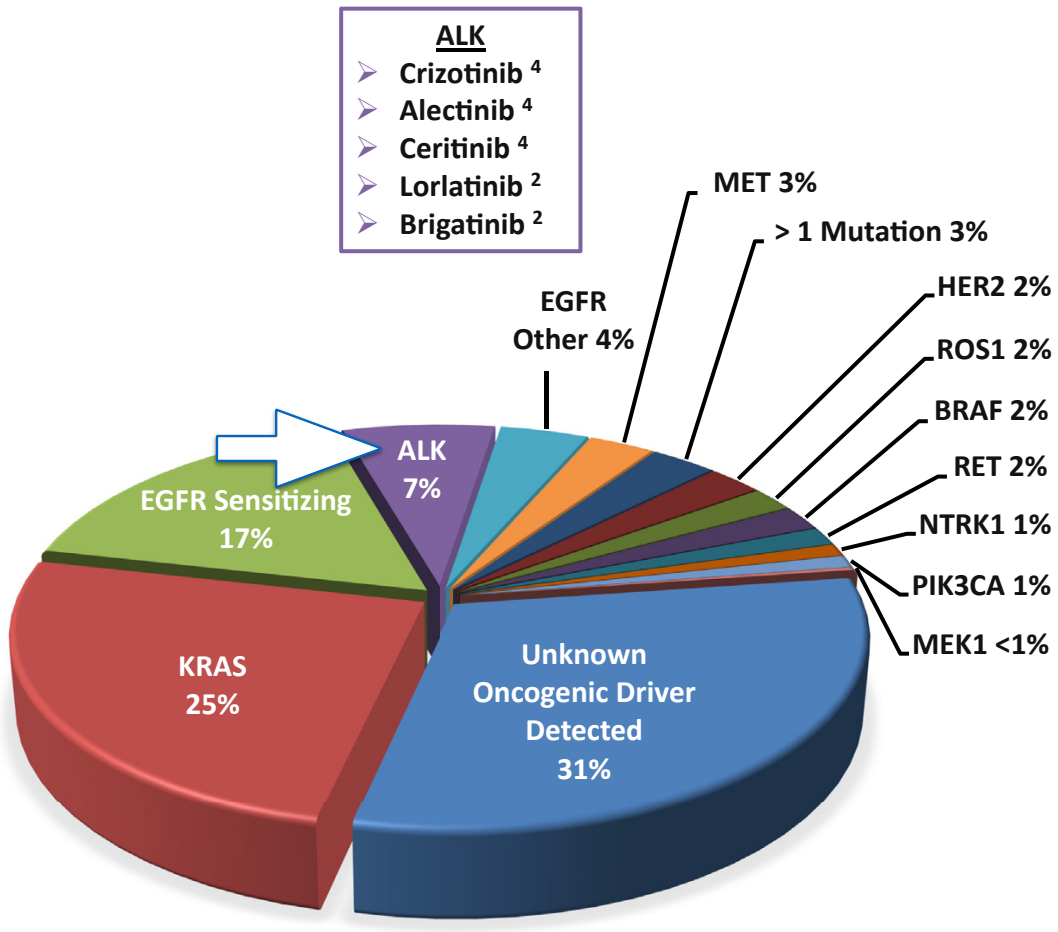
Analysis

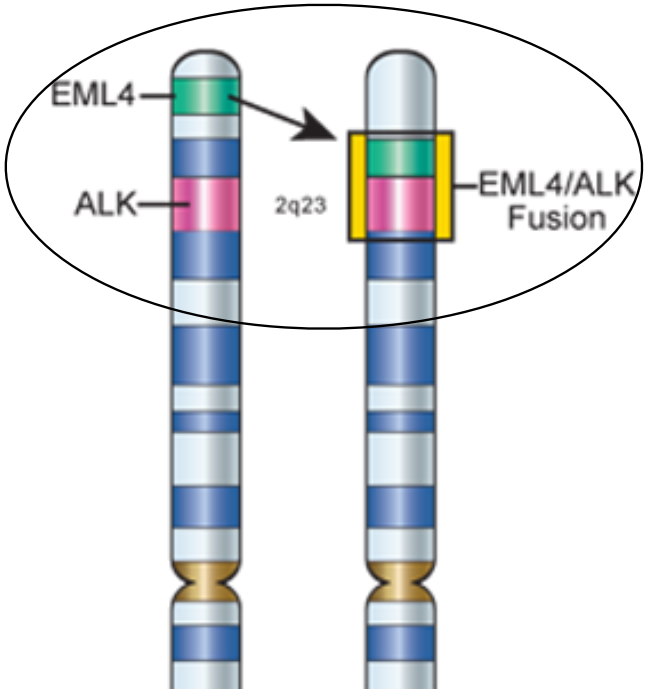


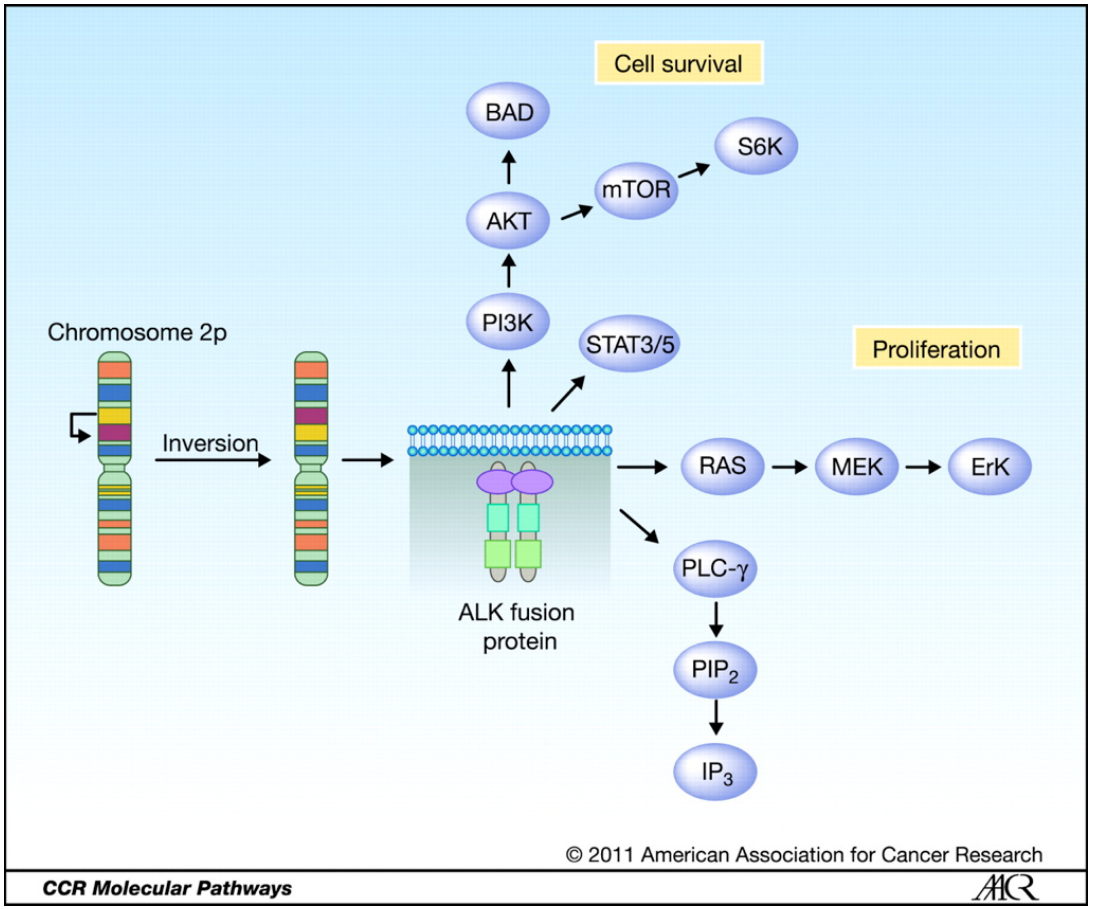
PCR bassed test



mutationspecific primer


ALK
Crizotinib 4
Alectinib 4
Ceritinib 4
Lorlatinib 2
Brigatinib 2
MET 3%
> 1 Mutation 3%
HER2 2%
ROS1 2%
BRAF 2%
RET 2%
NTRK1 1%
PIK3CA 1%
MEK1 <1%
EGFR
Other 4%
ALK
7%
EGFR Sensitizing
17%
KRAS
25%
Unknown
Oncogenic Driver
Detected
31%


EML4
ALK
2q23
EML4/ALK
Fusion


Cell survival
BAD
S6K
mTOR
AKT
PI3K
STAT3/5
Proliferation
Chromosome 2p
Inversion
RAS
MEK
ErK
PLC-γ
ALK fusion
protein
PIP2
IP3
© 2011 American Association for Cancer Research
CCR Molecular Pathways
AACR

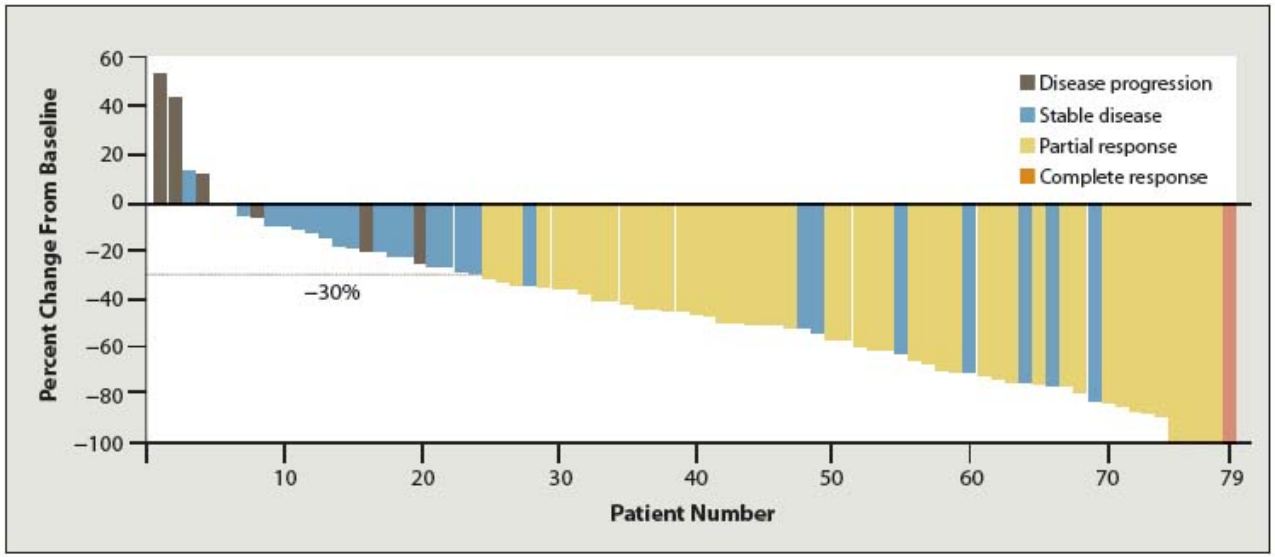
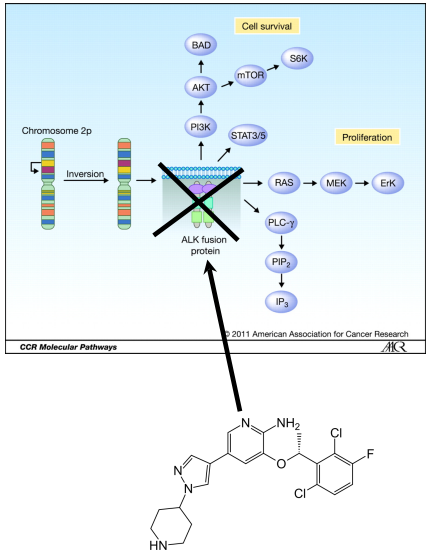
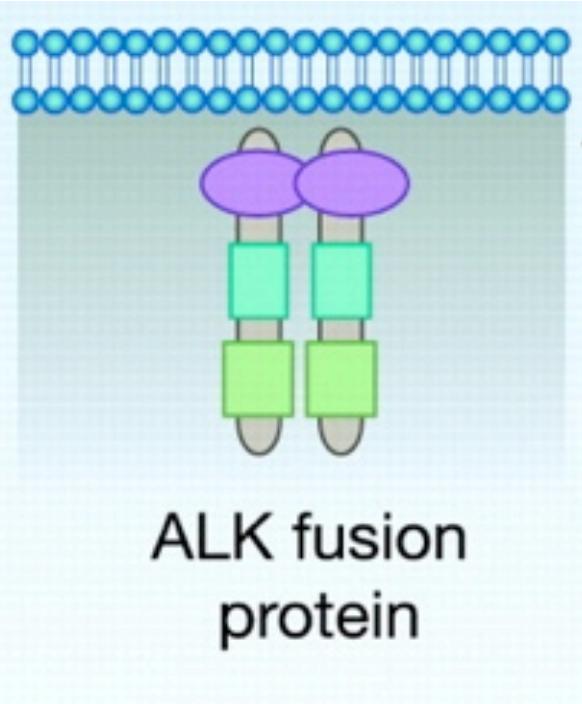


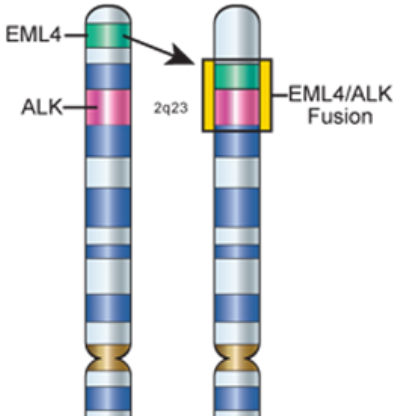
Figure 2: Waterfall plot showing response to crizotinib in patients with *EML4-ALK* NSCLC. Percent change in tumor burden relative to pretreatment baseline is represented. (Reproduced with permission from Kwak et al. N Engl J Med. 2010;363:1693-1703. Copyright © 2010, Massachusetts Medical Society.)



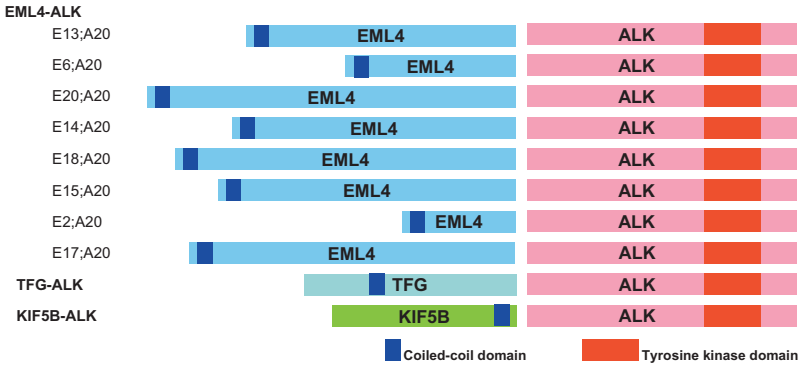
Detection of fusion protein



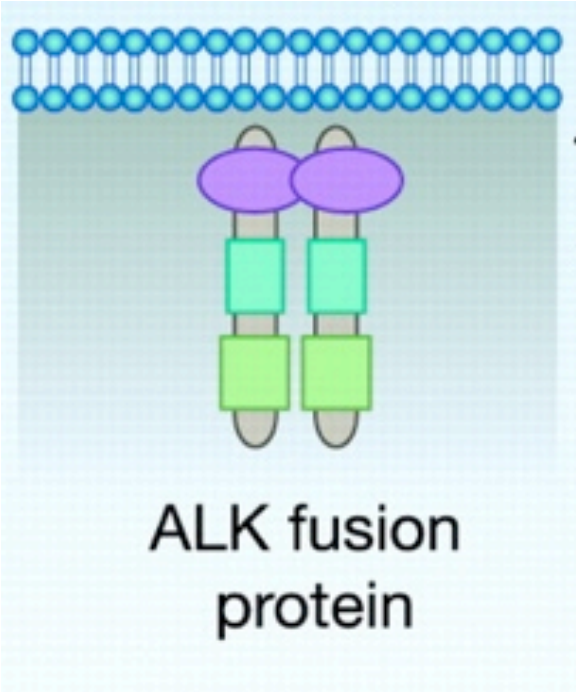
Detection of chromosomal changes



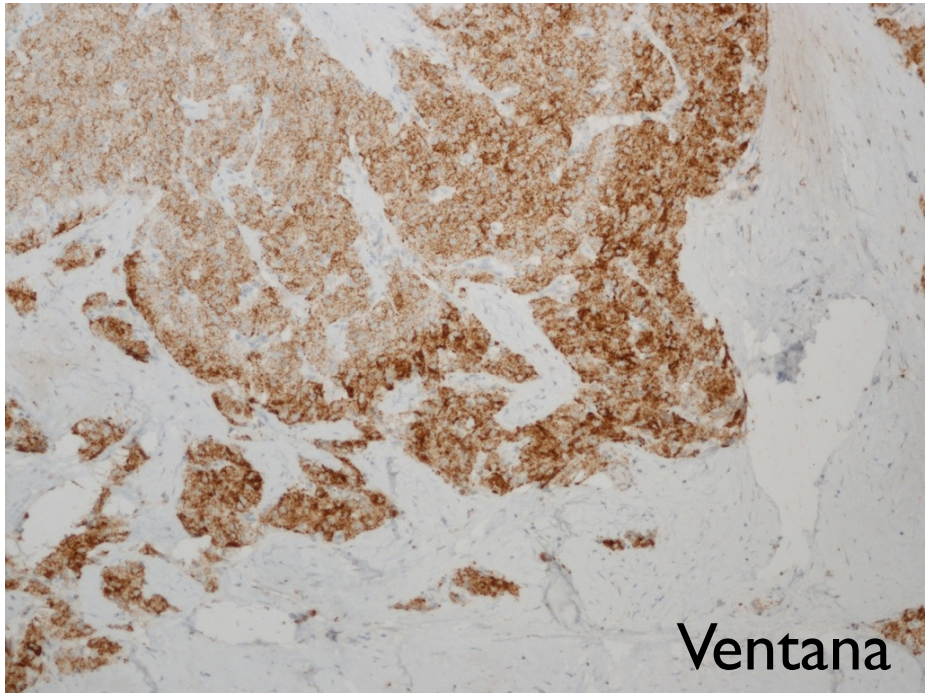
Detection of fusion RNA



Detection of fusion protein



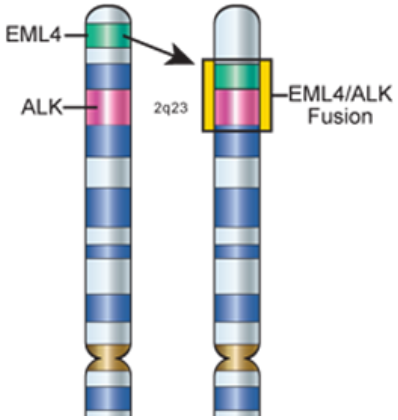
Immunohistochemistry



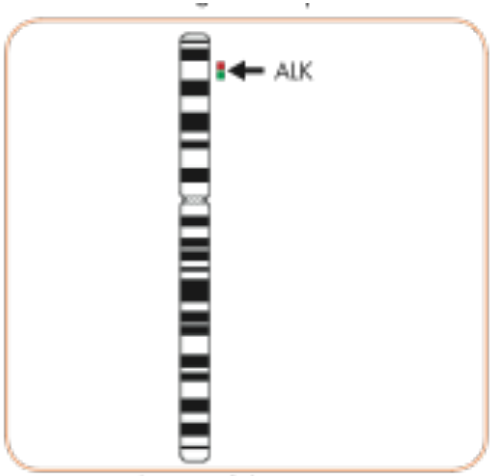
Detects ALK independent of fusion partner

Detection of chromosomal changes

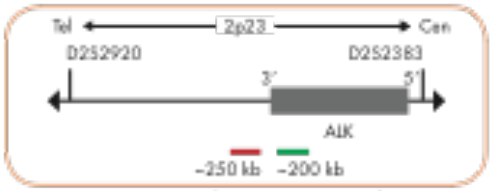
F(C)ISH



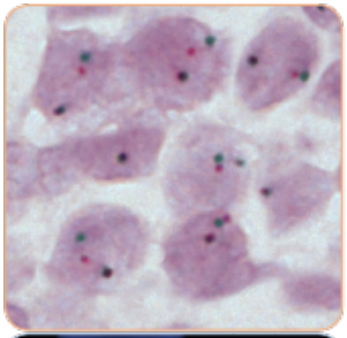
ZYTOVISION
Molecular diagnostics simplified

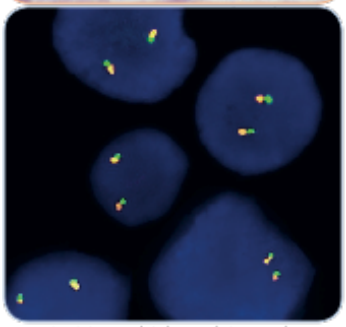


Ideogram of chromosome 2 indicating the hybridization locations.

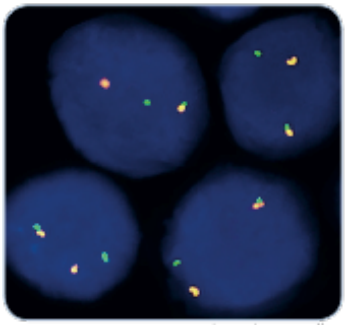


SPEC ALK Probe map (not to scale).

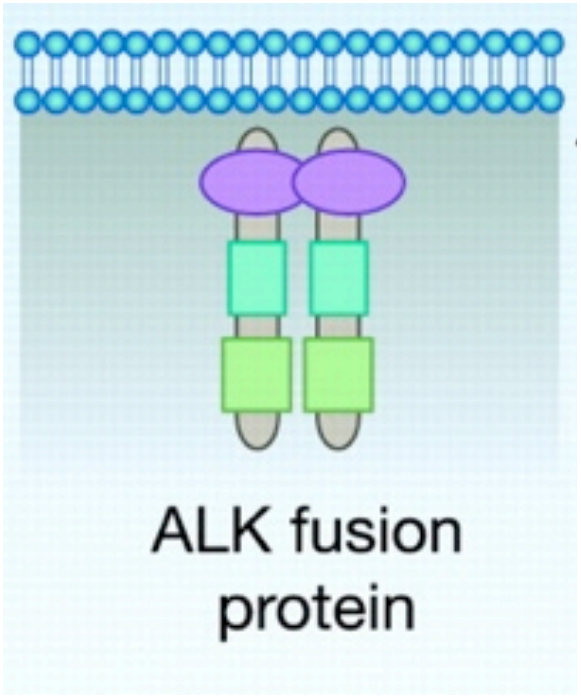




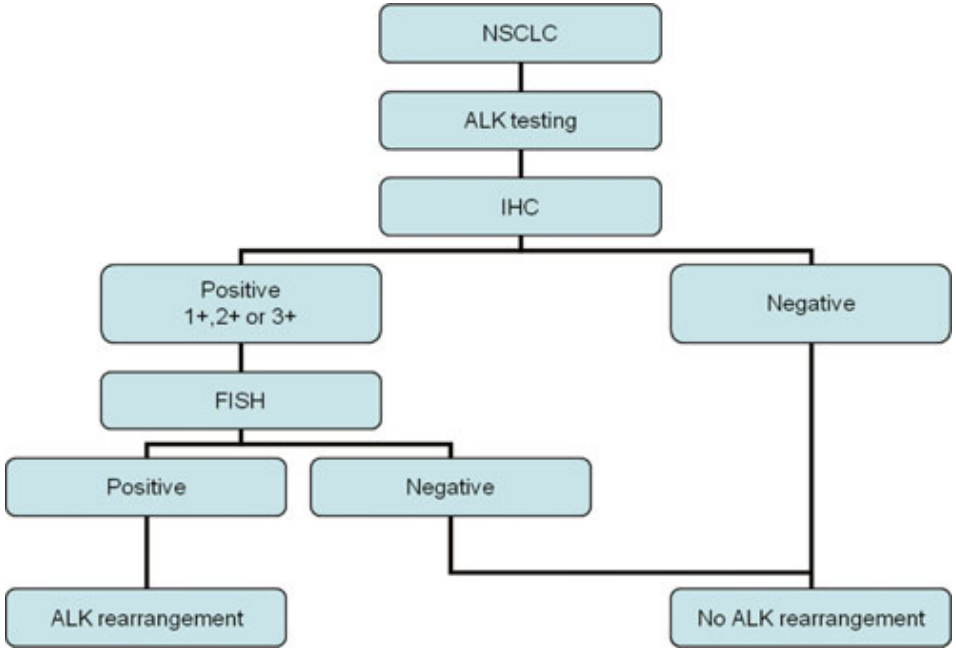
SPEC ALK Dual Color Break Apart Probe hybridized to normal interphase cells as indicated by two orange/green fusion signals per nucleus.



Detection of fusion protein



Algorithm



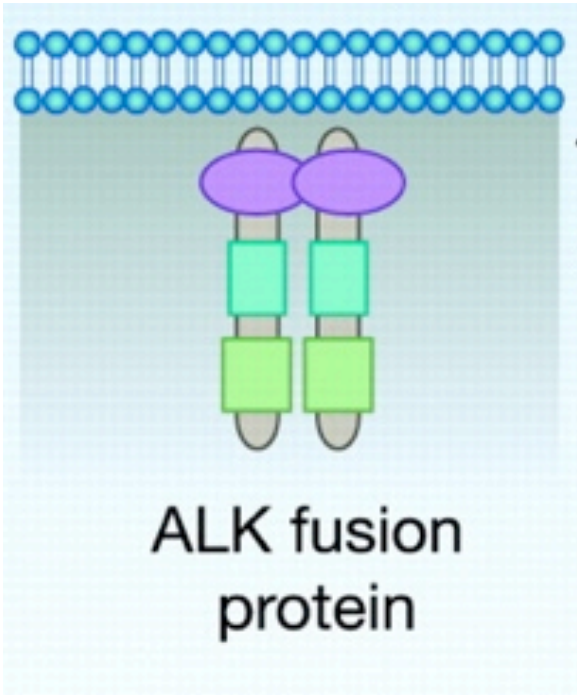
Virchows Arch (2012) 461:245–257
DOI 10.1007/s00428-012-1281-4

REVIEW AND PERSPECTIVES

EML4-ALK testing in non-small cell carcinomas of the lung: a review with recommendations

Erik Thunnissen · Lukas Bubendorf · Manfred Dietel · Göran Elmberger · Keith Kerr · Fernando Lopez-Rios · Holger Moch · Włodzimierz Olszewski · Patrick Pauwels · Frédérique Penault-Llorca · Giulio Rossi

Detection of fusion protein



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REVIEW AND PERSPECTIVES

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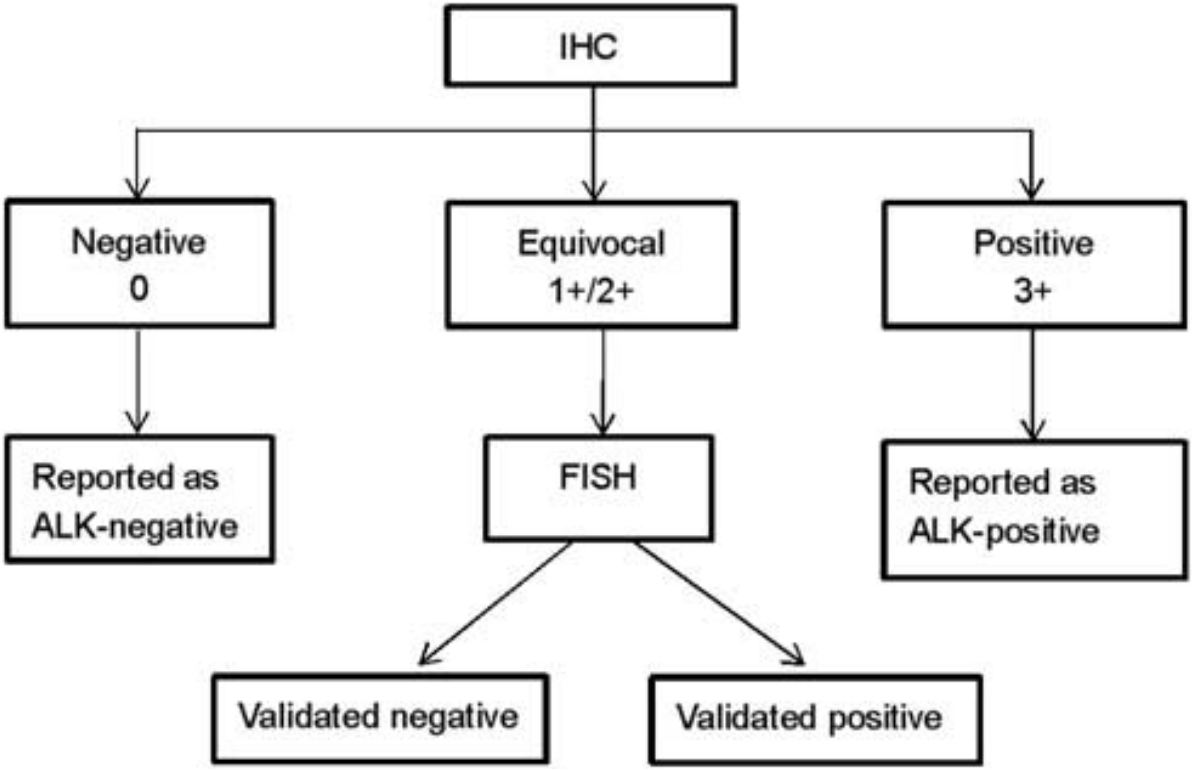
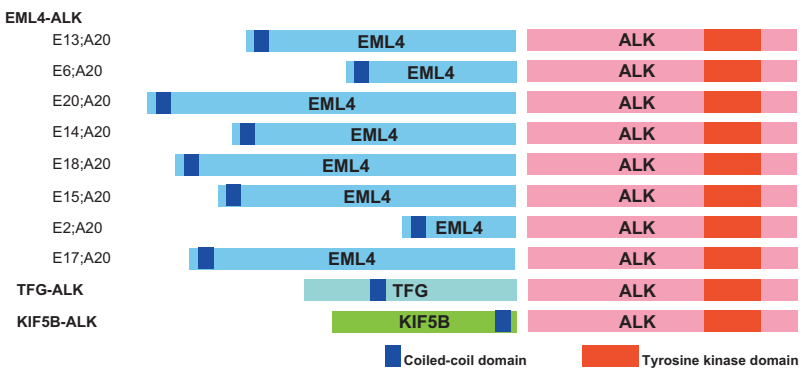
Algorithm



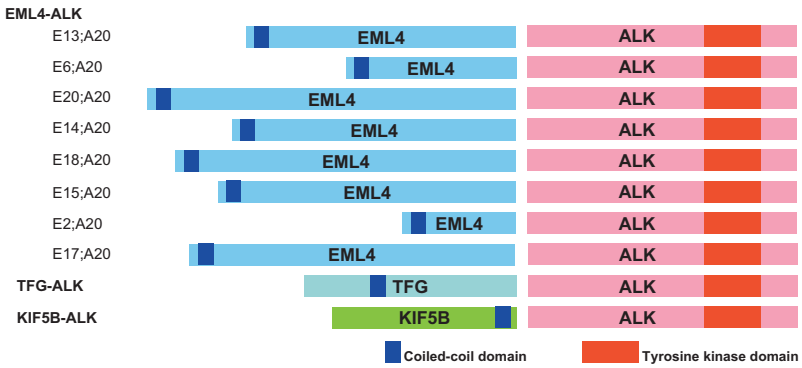
RT PCR based test

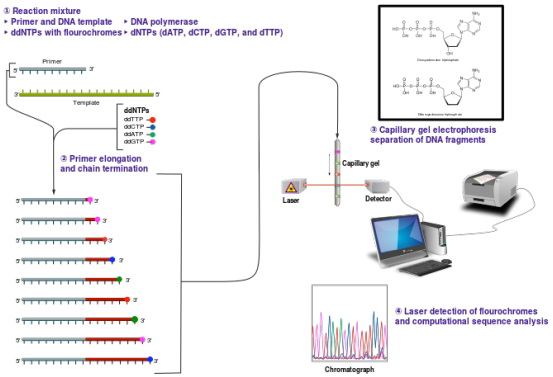
Detection of fusion RNA

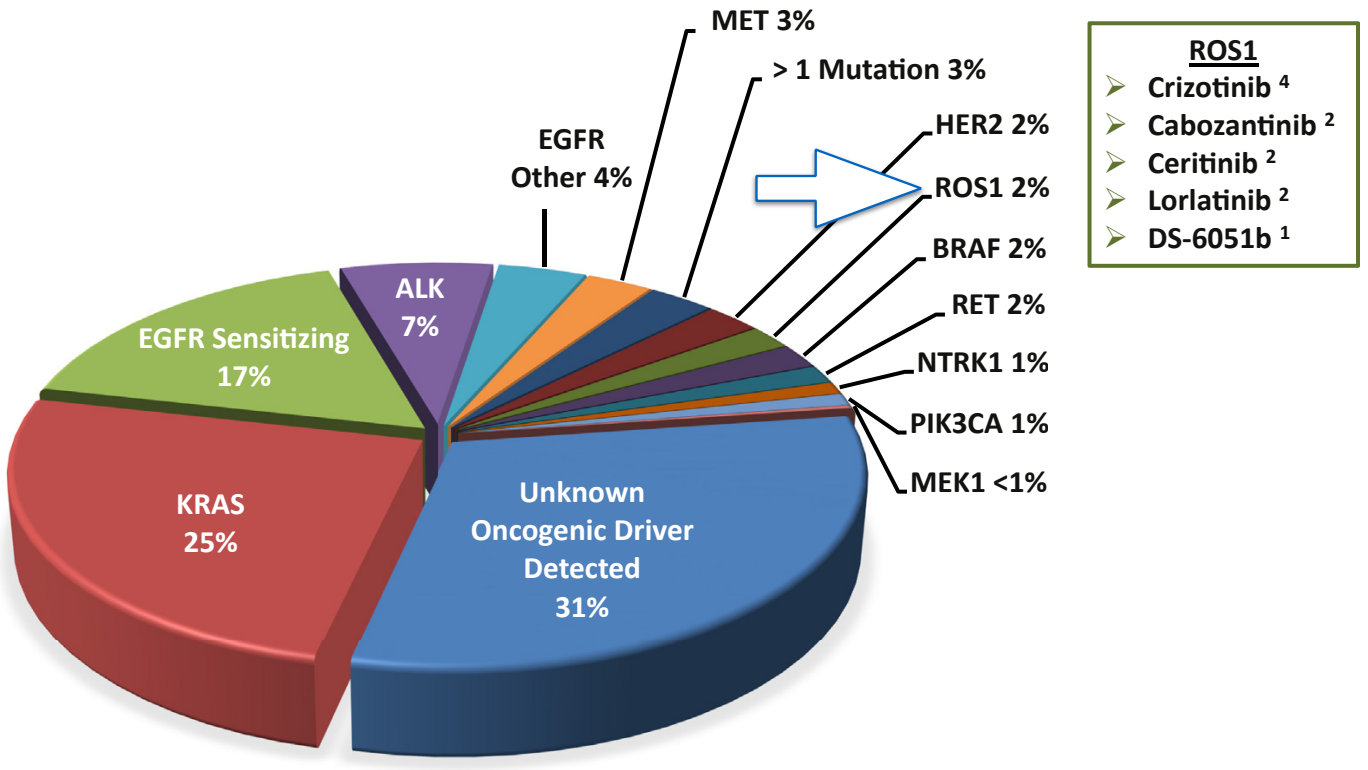


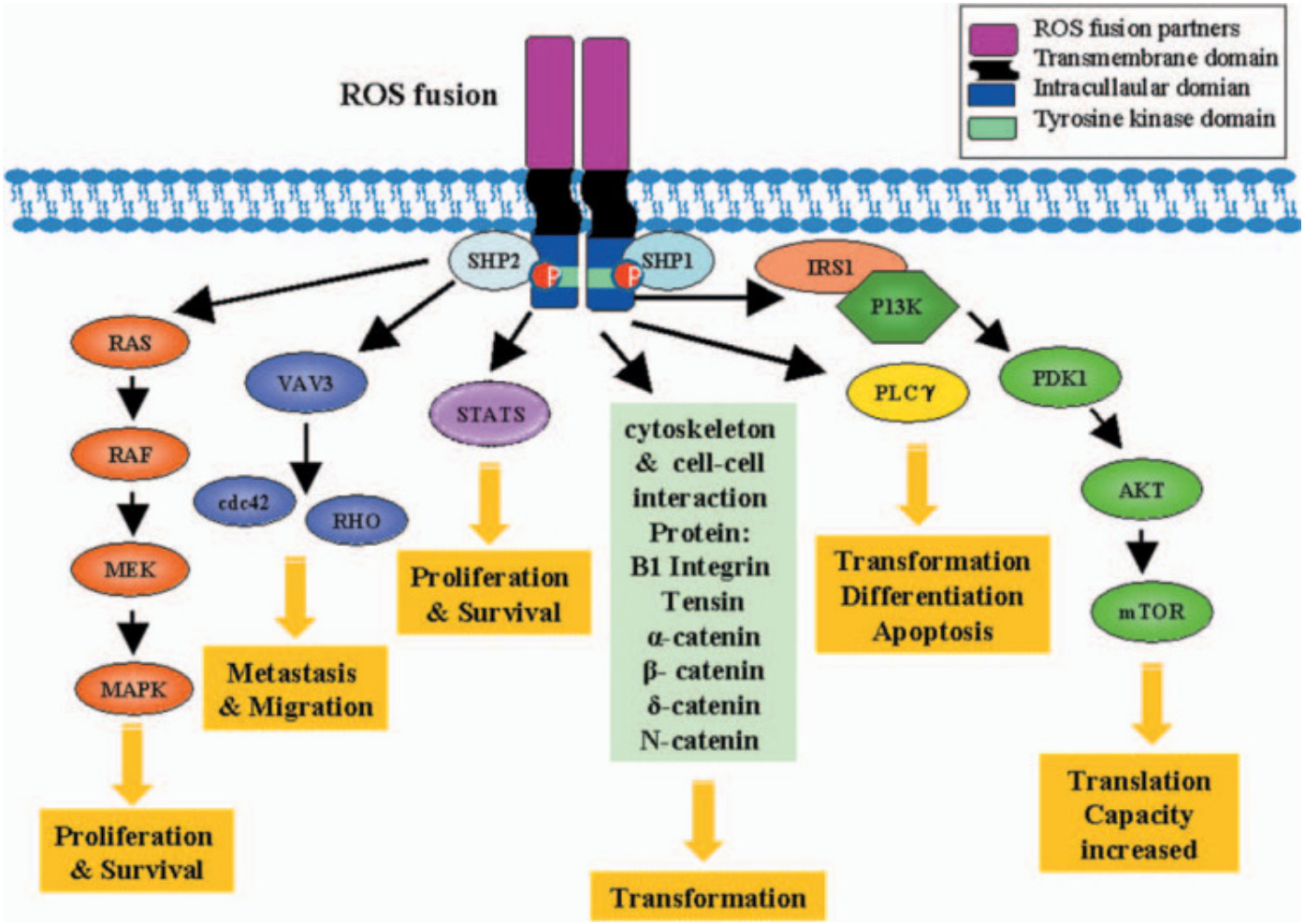
RNA Sequencing based test

Detection of fusion RNA



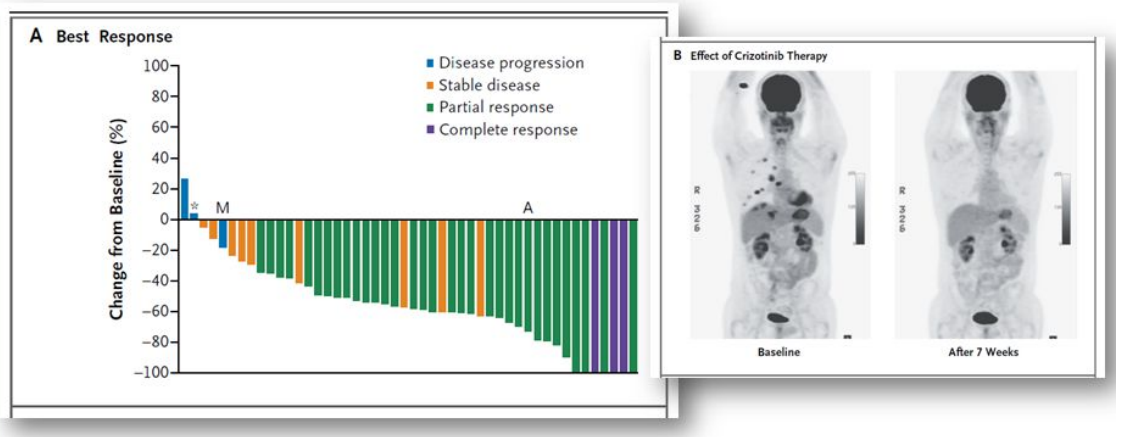



MET 3%
> 1 Mutation 3%
EGFR
Other 4%
HER2 2%
ROS1 2%
BRAF 2%
RET 2%
NTRK1 1%
PIK3CA 1%
MEK1 <1%
ALK
7%
EGFR Sensitizing
17%
KRAS
25%
Unknown
Oncogenic Driver
Detected
31%
ROS1
Crizotinib [4]
Cabozantinib [2]
Ceritinib [2]
Lorlatinib [2]
DS-6051b [1]


ROS fusion
ROS fusion partners
Transmembrane domain
Intracullaular domian
Tyrosine kinase domain
SHP2
SHP1
P
P
RAS
RAF
MEK
MAPK
Proliferation & Survival
VAV3
cdc42
RHO
Metastasis & Migration
STATS
Proliferation & Survival
cytoskeleton & cell-cell interaction Protein:
B1 Integrin
Tensin
α-catenin
β- catenin
δ-catenin
N-catenin
Transformation
IRS1
P13K
PLCγ
Transformation Differentiation Apoptosis
PDK1
AKT
mTOR
Translation Capacity increased

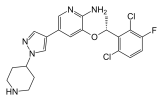
UNIVERSITY OF TORINO – DEPARTMENT OF ONCOLOGY

Tumor responses to crizotinib in ROS1-rearranged NSCLC



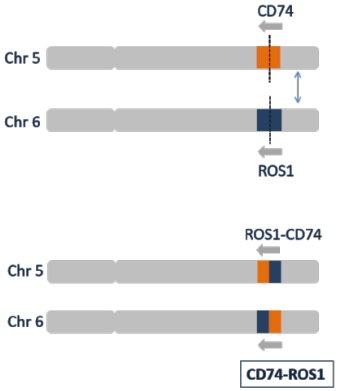
Overall response rate 72% (6% CR, 66% PR).
Median time to response 7.9 weeks (range, 4.3 - 32.0)

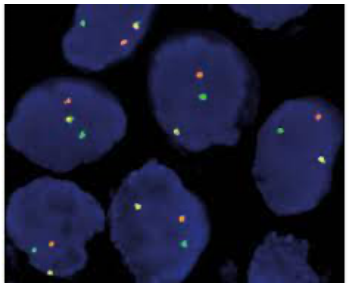
Shaw AT et al, N Engl J Med 2014;371:1963-71.



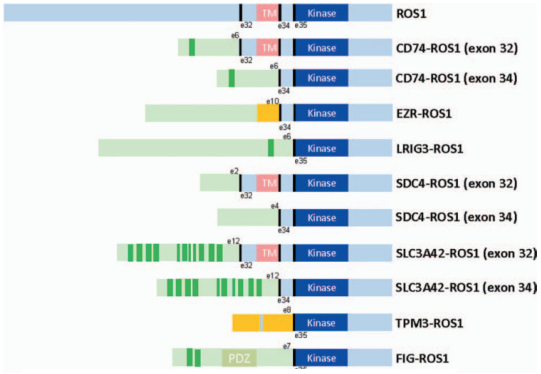
NordiQC

Detection of chromosomal changes

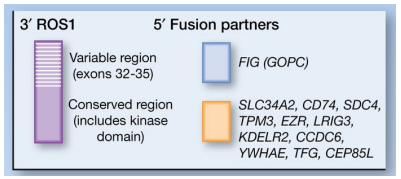


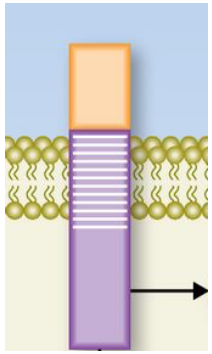


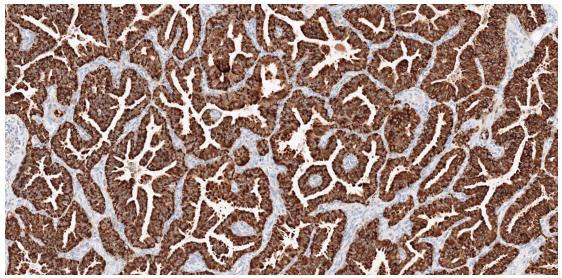
Detection of fusion RNA



Detection of fusion protein



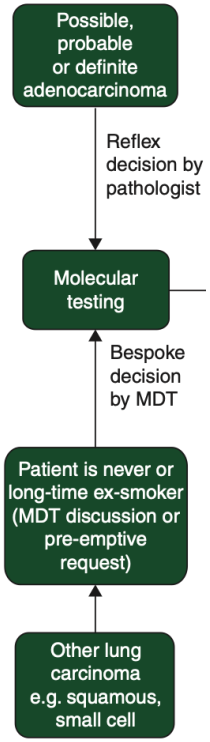




Suggestion

NordIQC

Next generation seq.



FFPE

Quality
Tumor cell %

DNA workflow

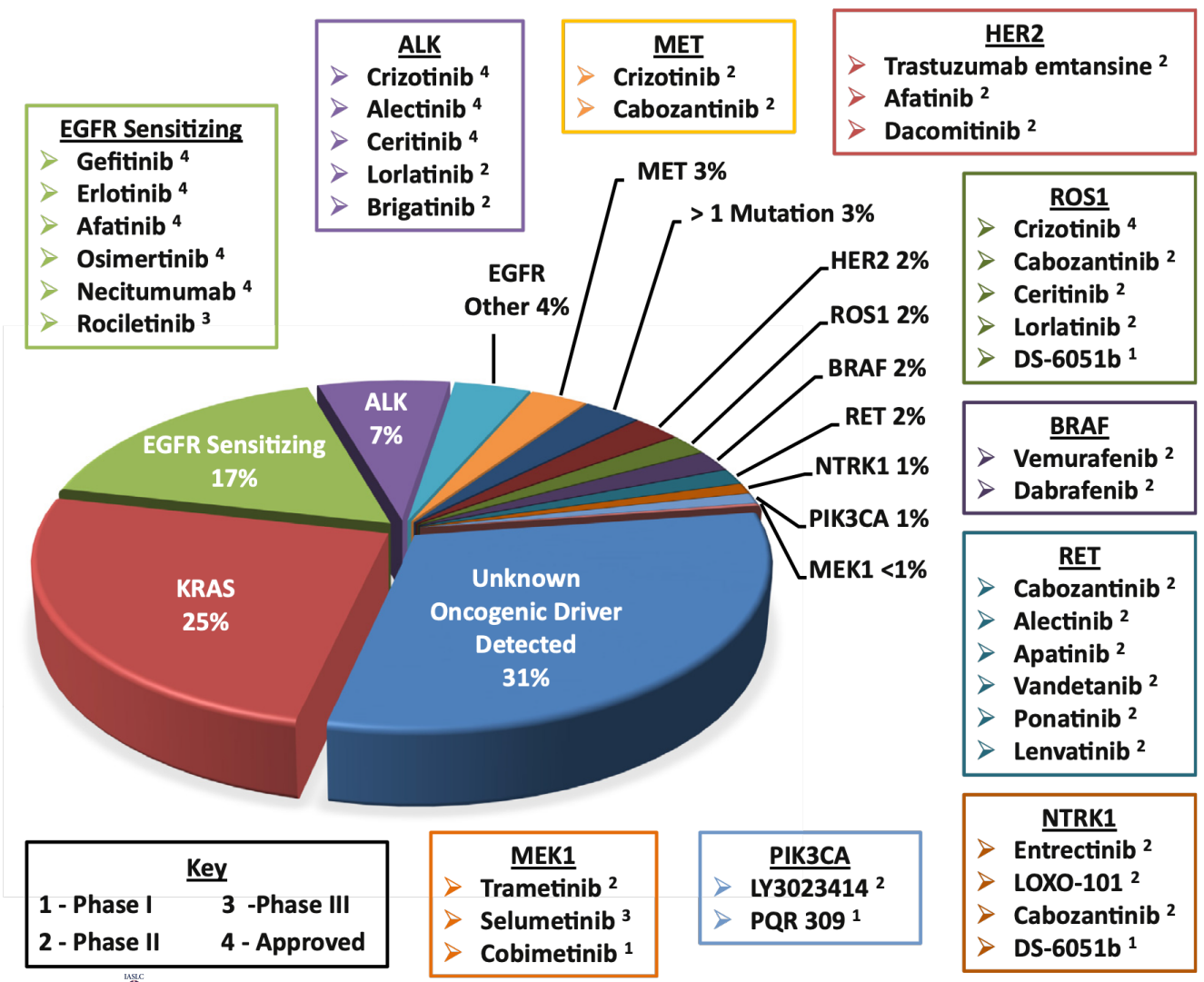
DNA purification | Sequencing | Library prep. | Variant calling (Bioinformatics)

EGFR

RNA workflow

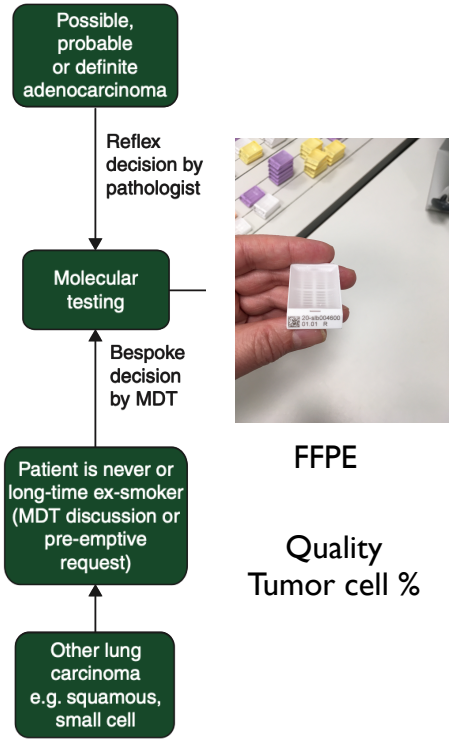
RNA purification | Sequencing | Library prep. | Variant calling (Bioinformatics)

ALK, ROS1


EGFR Sensitizing
Gefitinib 4
Erlotinib 4
Afatinib 4
Osimertinib 4
Necitumumab 4
Rociletinib 3
ALK
Crizotinib 4
Alectinib 4
Ceritinib 4
Lorlatinib 2
Brigatinib 2
MET
Crizotinib 2
Cabozantinib 2
HER2
Trastuzumab emtansine 2
Afatinib 2
Dacomitinib 2
ROS1
Crizotinib 4
Cabozantinib 2
Ceritinib 2
Lorlatinib 2
DS-6051b 1
BRAF
Vemurafenib 2
Dabrafenib 2
RET
Cabozantinib 2
Alectinib 2
Apatinib 2
Vandetanib 2
Ponatinib 2
Lenvatinib 2
NTRK1
Entrectinib 2
LOXO-101 2
Cabozantinib 2
DS-6051b 1
MEK1
Trametinib 2
Selumetinib 3
Cobimetinib 1
PIK3CA
LY3023414 2
PQR 309 1
Key
1 - Phase I
2 - Phase II
3 -Phase III
4 - Approved
EGFR Sensitizing 17%
ALK 7%
KRAS 25%
Unknown Oncogenic Driver Detected 31%
EGFR Other 4%
MET 3%
> 1 Mutation 3%
HER2 2%
ROS1 2%
BRAF 2%
RET 2%
NTRK1 1%
PIK3CA 1%
MEK1 <1%

Suggestion

Next generation seq.



FFPE

Quality
Tumor cell %

DNA workflow

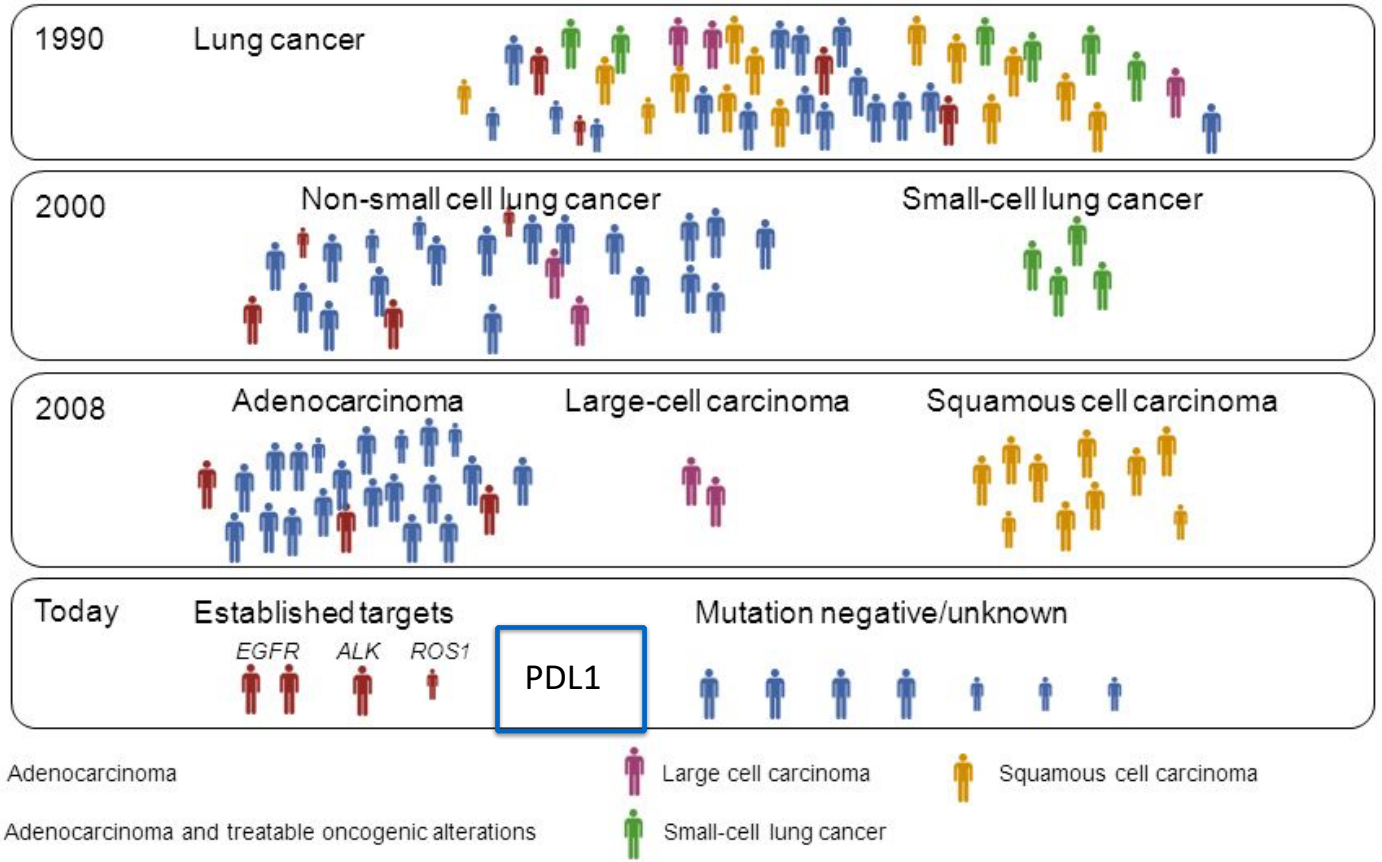
DNA purification | Sequencing | Library prep. | Variant calling (Bioinformatics)

RNA workflow

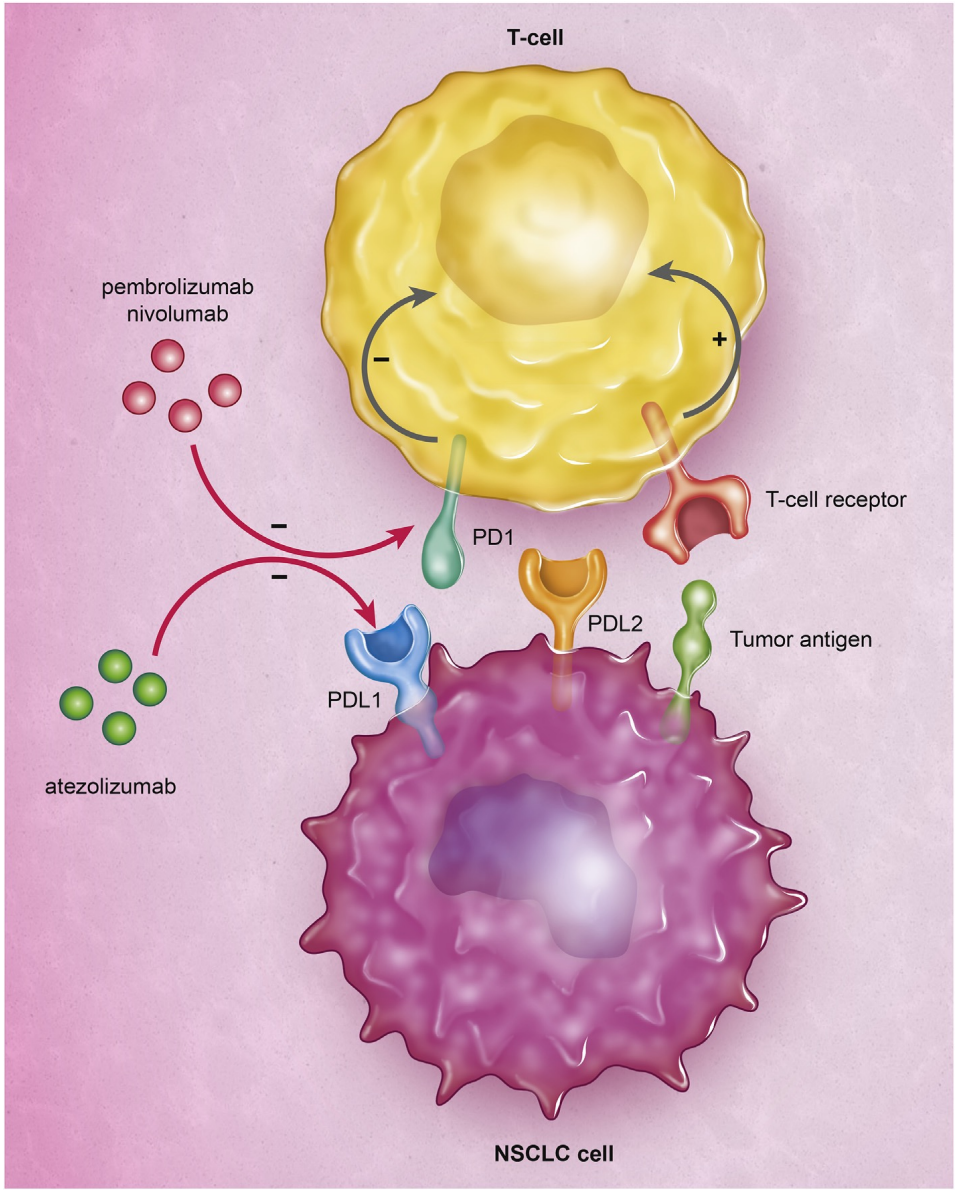
RNA purification | Sequencing | Library prep. | Variant calling (Bioinformatics)

Comprehensive Result

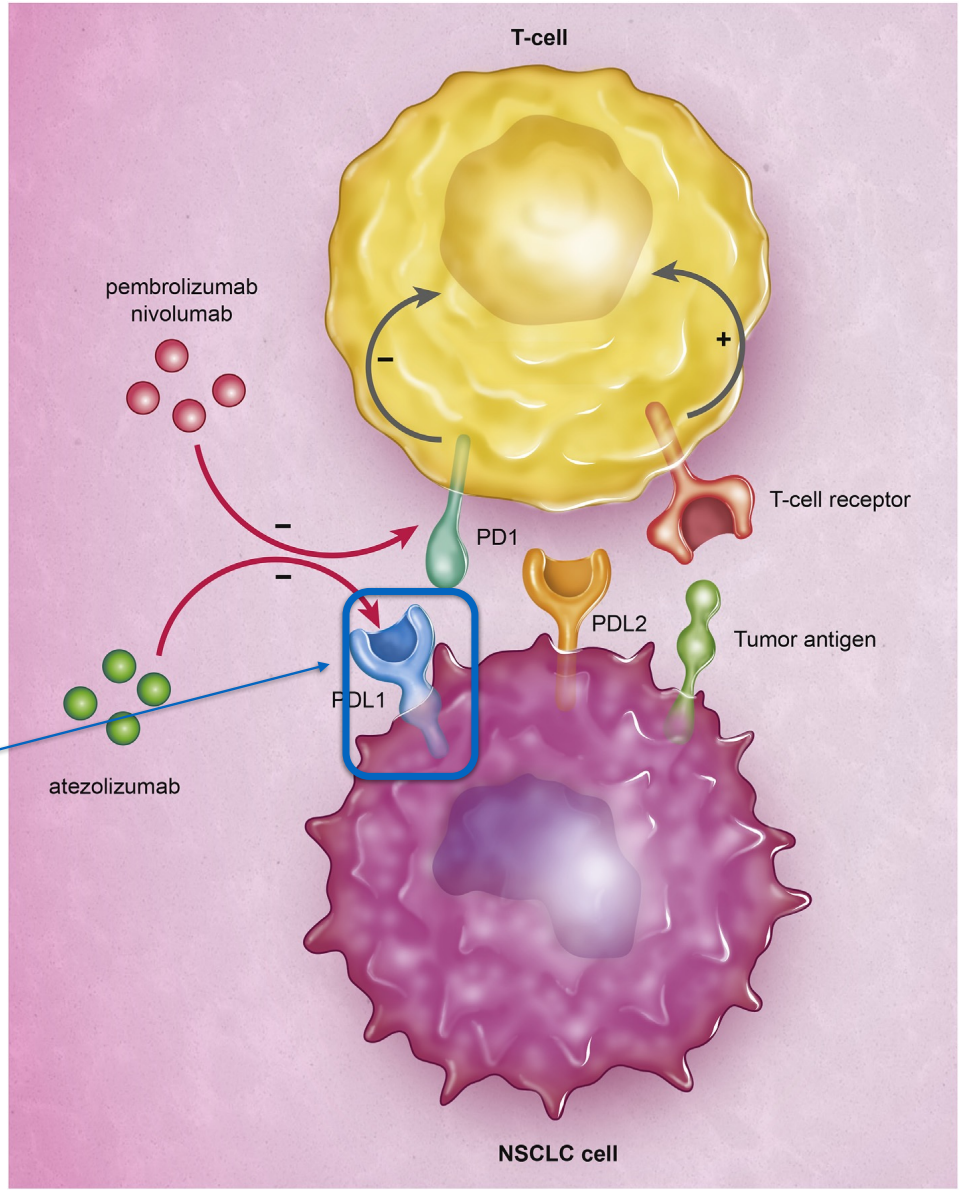
Patient selection in lung cancer: Evolution over time

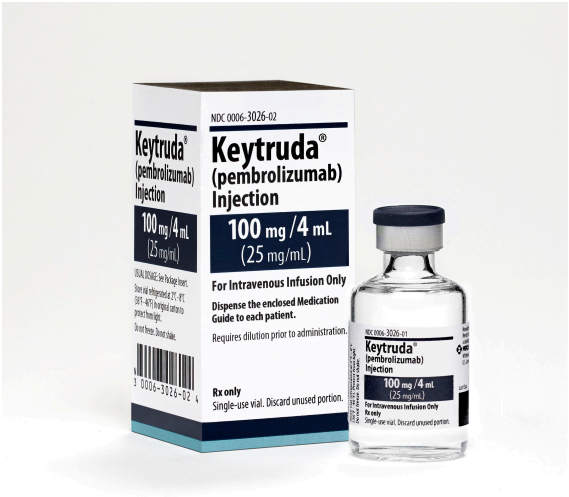


Adapted from Reck M, et al. Lancet 2013;382:709–19


T-cell
pembrolizumab
nivolumab
–
+
–
PD1
T-cell receptor
–
PDL2
Tumor antigen
PDL1
atezolizumab
NSCLC cell

Predictive marker





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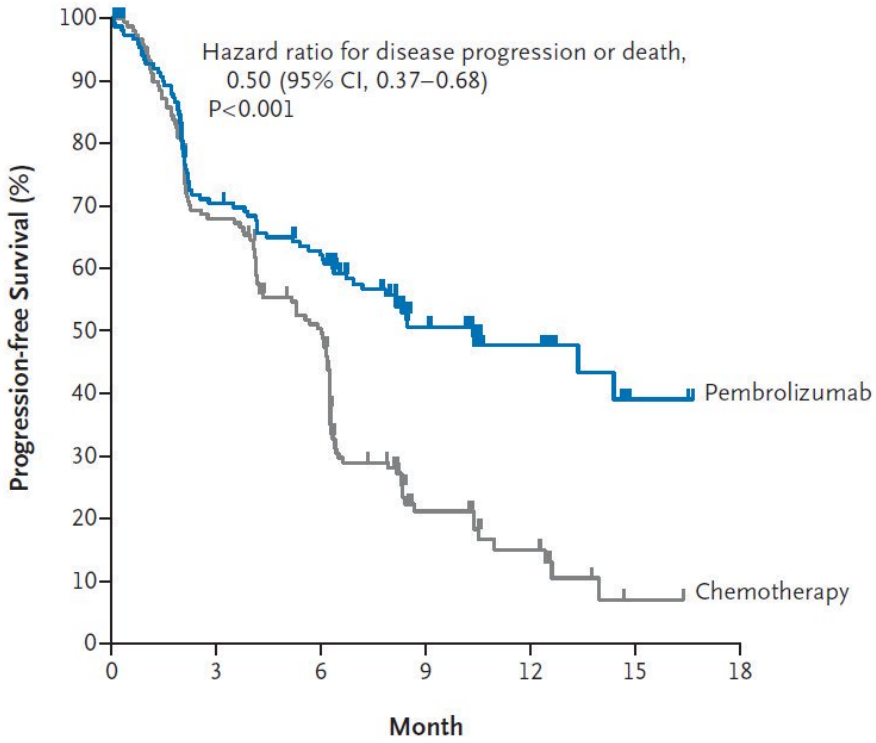
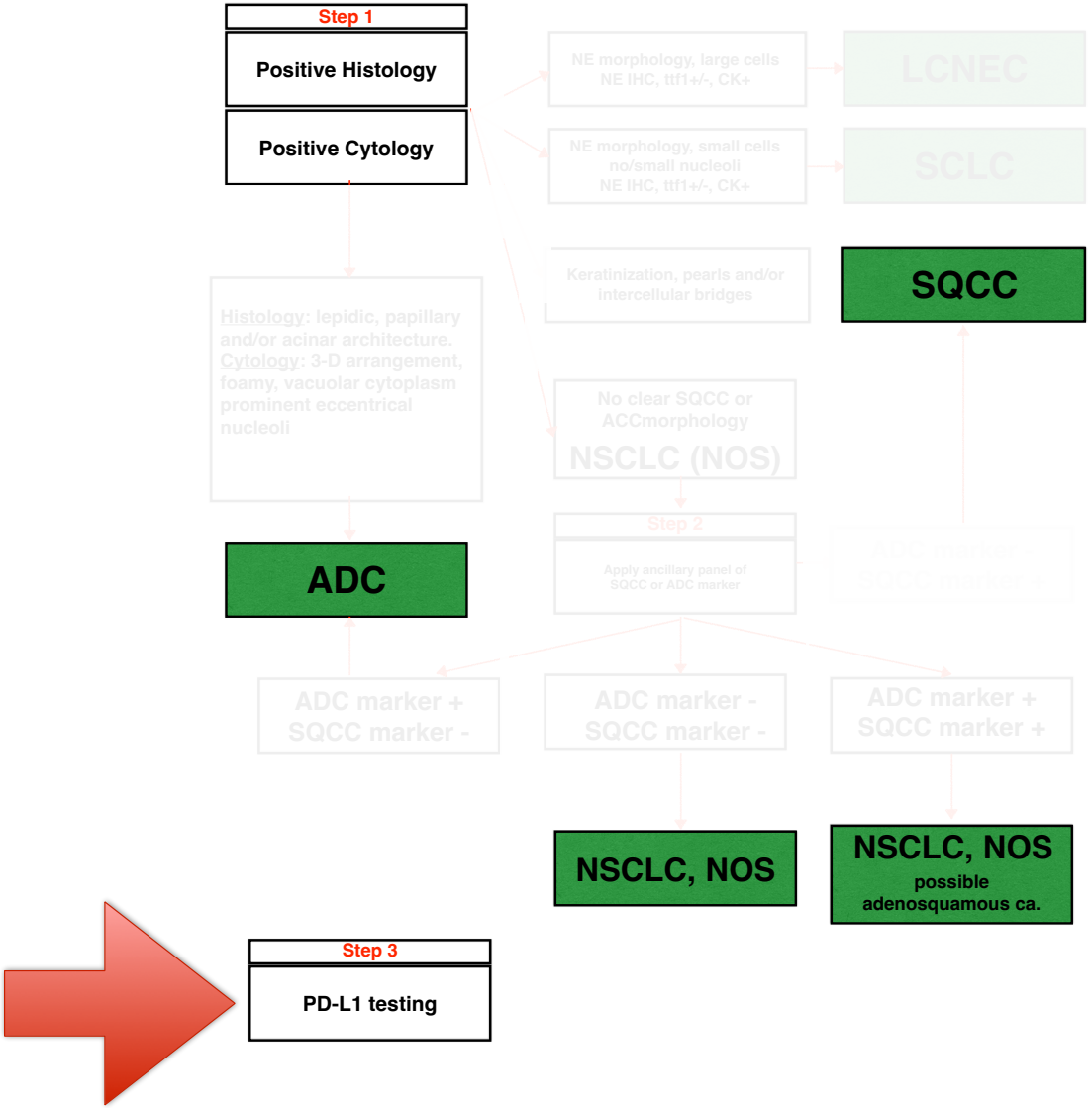
Pembrolizumab versus Chemotherapy for PD-L1–Positive Non–Small-Cell Lung Cancer

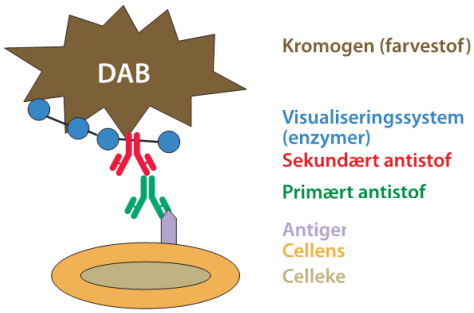
Martin Reck, M.D., Ph.D., Delvys Rodríguez-Abreu, M.D., Andrew G. Robinson, M.D., Rina Hui, M.B., B.S., Ph.D., Tibor Csőszi, M.D., Andrea Fülöp, M.D., Maya Gottfried, M.D., Nir Peled, M.D., Ph.D., Ali Tafreshi, M.D., Sinead Cuffe, M.D., Mary O'Brien, M.D., Suman Rao, M.D., Katsuyuki Hotta, M.D., Ph.D., Melanie A. Leiby, Ph.D., Gregory M. Lubiniecki, M.D., Yue Shentu, Ph.D., Reshma Rangwala, M.D., Ph.D., and Julie R. Brahmer, M.D., for the KEYNOTE-024 Investigators*



No. at Risk

Pembrolizumab	154	104	89	44	22	3	1
Chemotherapy	151	99	70	18	9	1	0

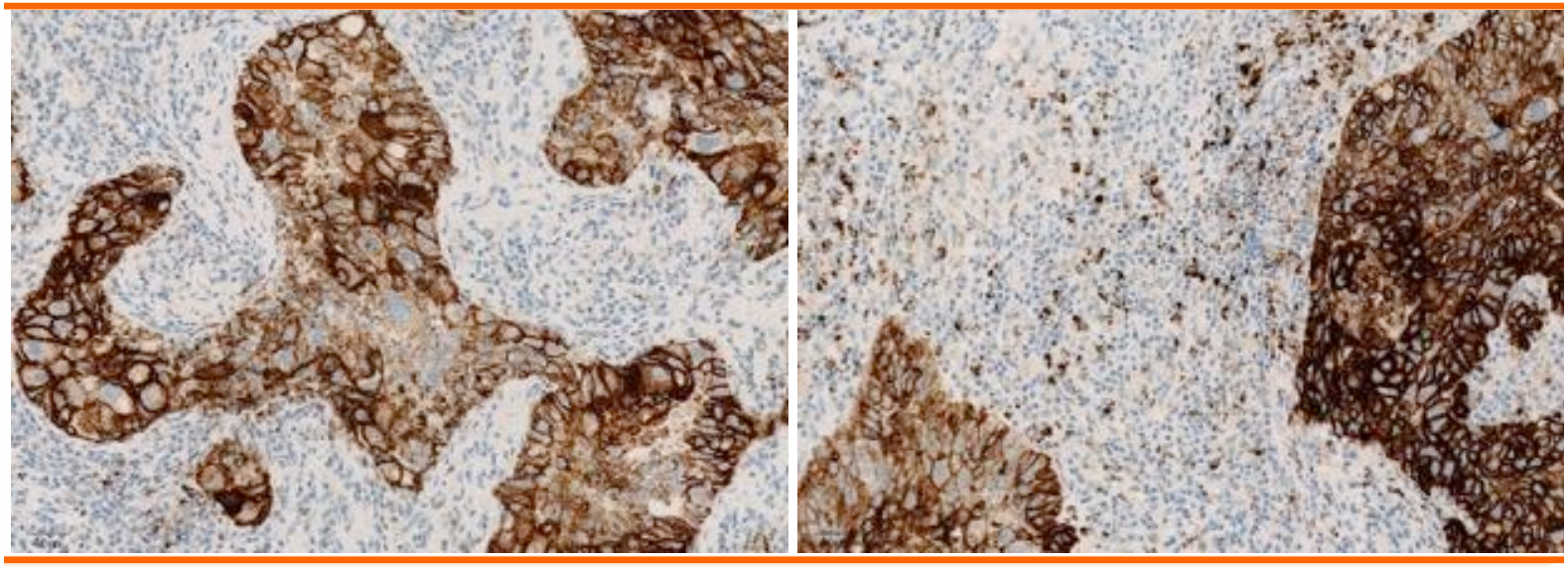

Step 1
Positive Histology
Positive Cytology
NE morphology, large cells
NE IHC, ttf1+/-, CK+
LCNEC
NE morphology, small cells
no/small nucleoli
NE IHC, ttf1+/-, CK+
SCLC
Keratinization, pearls and/or
intercellular bridges
SQCC
Histology: lepidic, papillary
and/or acinar architecture.
Cytology: 3-D arrangement,
foamy, vacuolar cytoplasm
prominent eccentrical
nucleoli
No clear SQCC or
ACCmorphology
NSCLC (NOS)
Step 2
Apply ancillary panel of
SQCC or ADC marker
ADC marker -
SQCC marker +
ADC
ADC marker +
SQCC marker -
ADC marker -
SQCC marker -
ADC marker +
SQCC marker +
NSCLC, NOS
NSCLC, NOS
possible
adenosquamous ca.
Step 3
PD-L1 testing



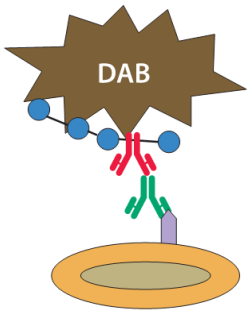
NordiQC

Tumor cells (TCs)

Tumor and immune cells (TCs and ICs)



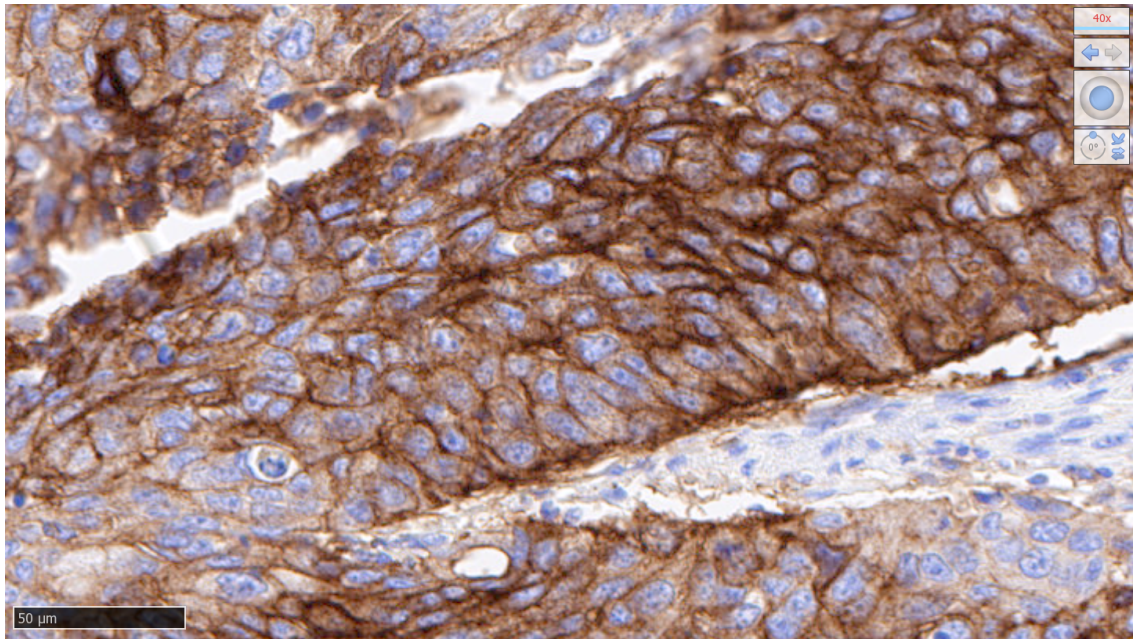
Immunhistological staining for PDL1



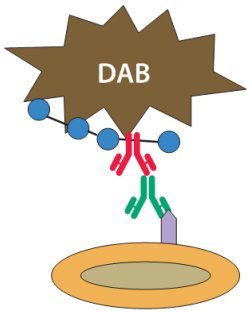
Kromogen (farvestof)

Visualiseringssystem (enzymer)
Sekundært antistof
Primært antistof

Antigen
Cellens cytoplasma
Cellekerne



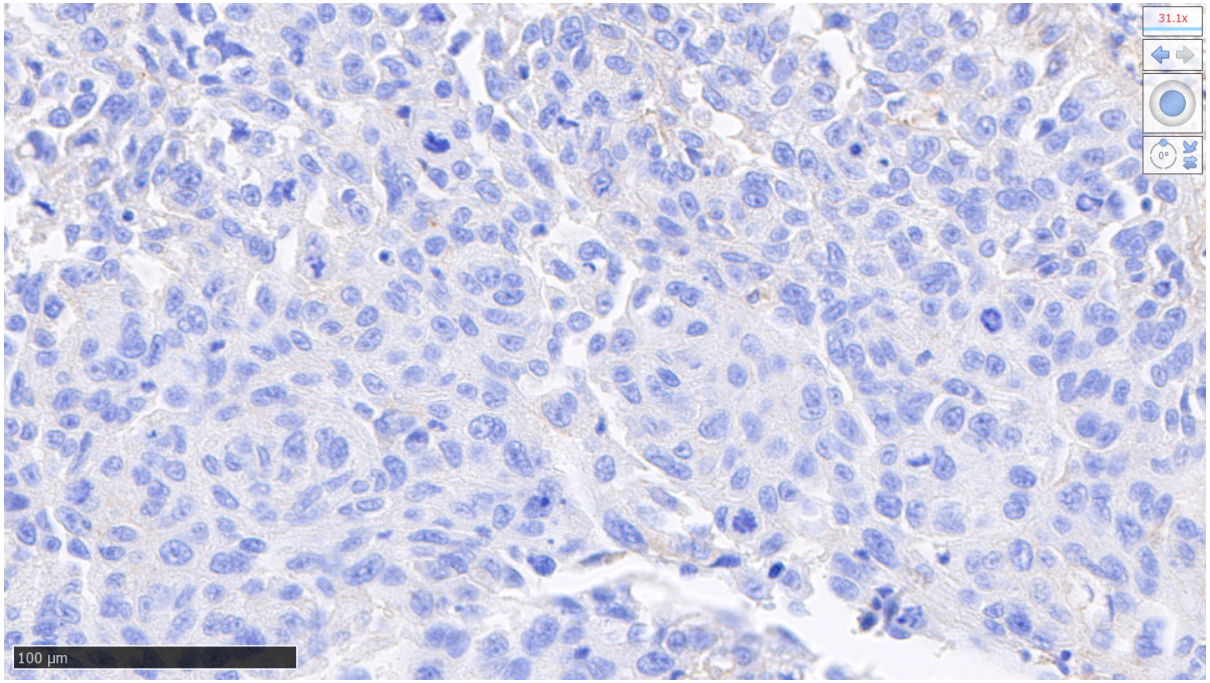
Biopsy NSCLC 100% TPS



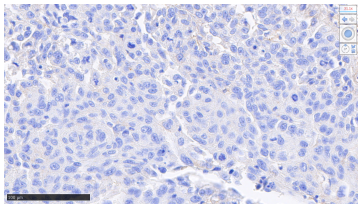
Kromogen (farvestof)

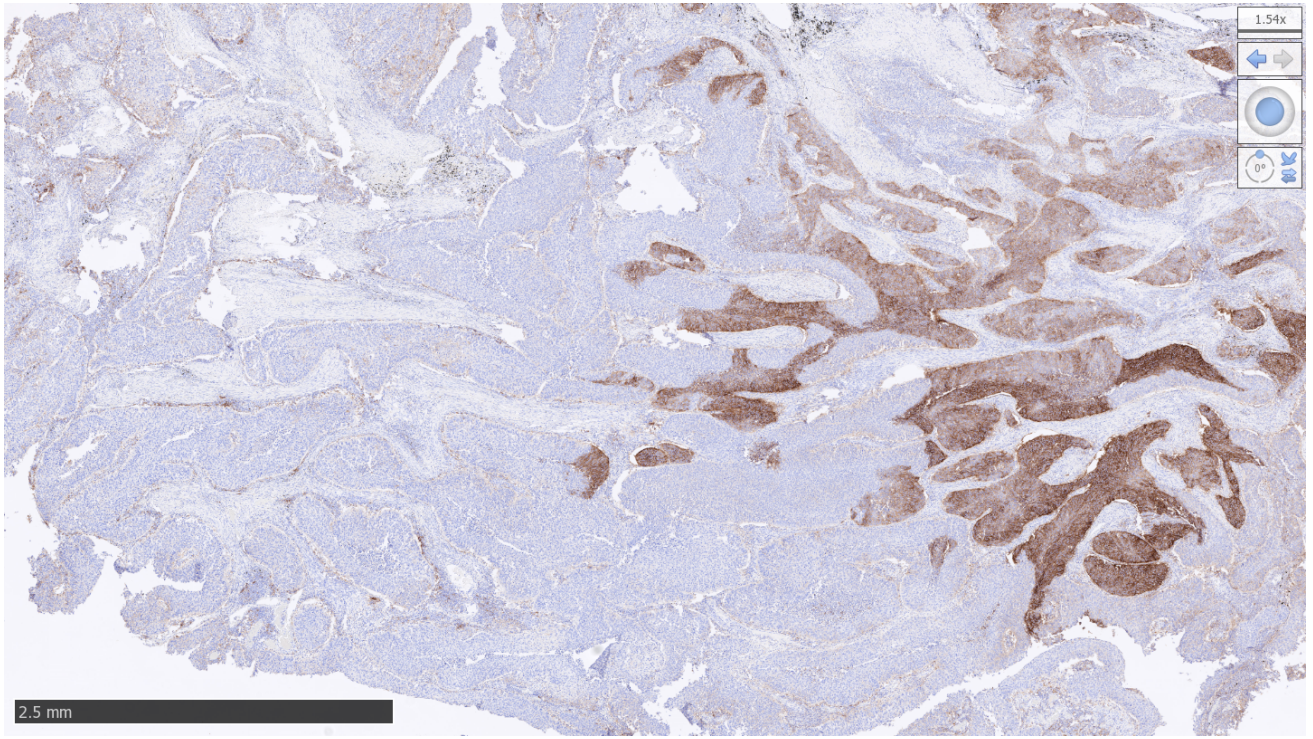
Visualiseringssystem (enzymer)
Sekundært antistof
Primært antistof

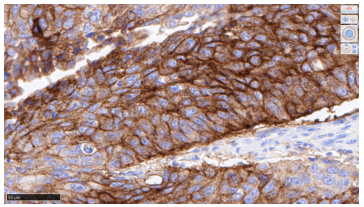
Antigen
Cellens cytoplasma
Cellekerne



Biopsy NSCLC 0% TPS



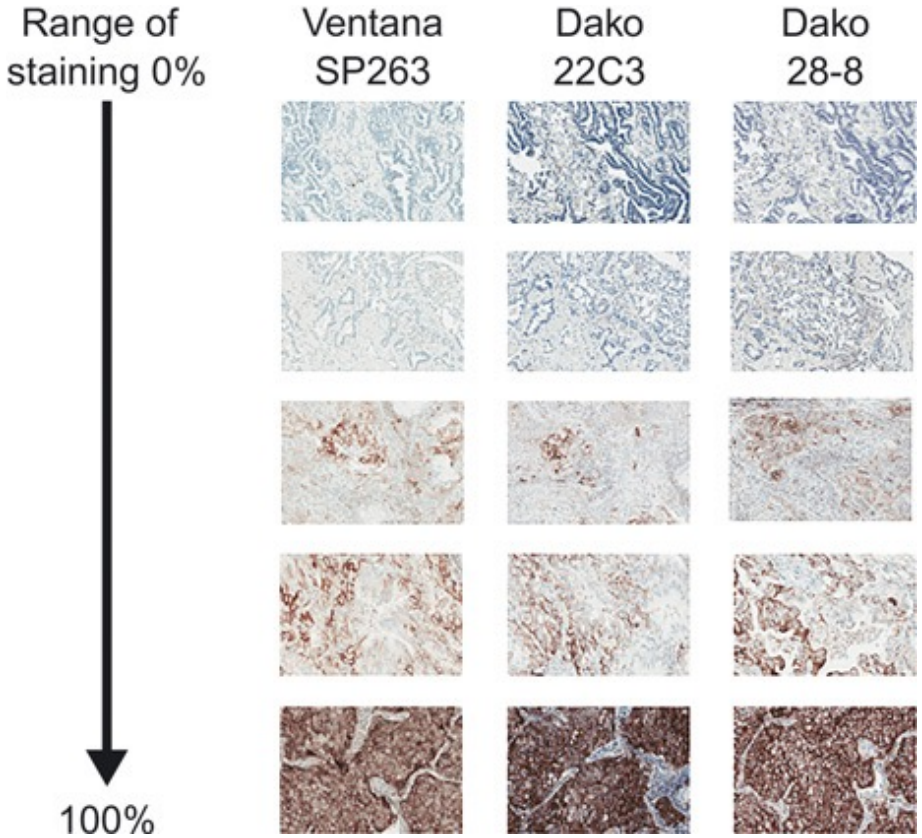

1.54x
2.5 mm



Test	Ventana SP263 (1)	Dako 22C3 (2)	Dako 28-8 (3)	Ventana SP142 (4)
Developed as companion diagnostic assay for:	Durvalumab (AstraZeneca/ MedImmune)	Pembrolizumab (Merck Sharp & Dohme)	Nivolumab (Bristol-Myers Squibb)	Atezolizumab (Genentech)
Instrument	VENTANA BenchMark ULTRA	Dako Autostainer Link 48	Dako Autostainer Link 48	VENTANA BenchMark ULTRA
PD-L1 antibody	Clone SP263 (rabbit monoclonal)	Clone 22C3 (mouse monoclonal)	Clone 28-8 (rabbit monoclonal)	Clone SP142 (rabbit monoclonal)
Compartment	Tumor cell membrane	Tumor cell membrane	Tumor cell membrane	Tumor cells and tumor-infiltrating immune cells
Cut-off(s) for high PD-L1 expression	≥25% of tumor cells (5)	≥1%; ≥50% of tumor cells (6)	≥1%; ≥5%; ≥10% of tumor cells (7)	≥50% of tumor cells or ≥10% of tumor area with immune cells (if <50% of tumor

SP142

TPS



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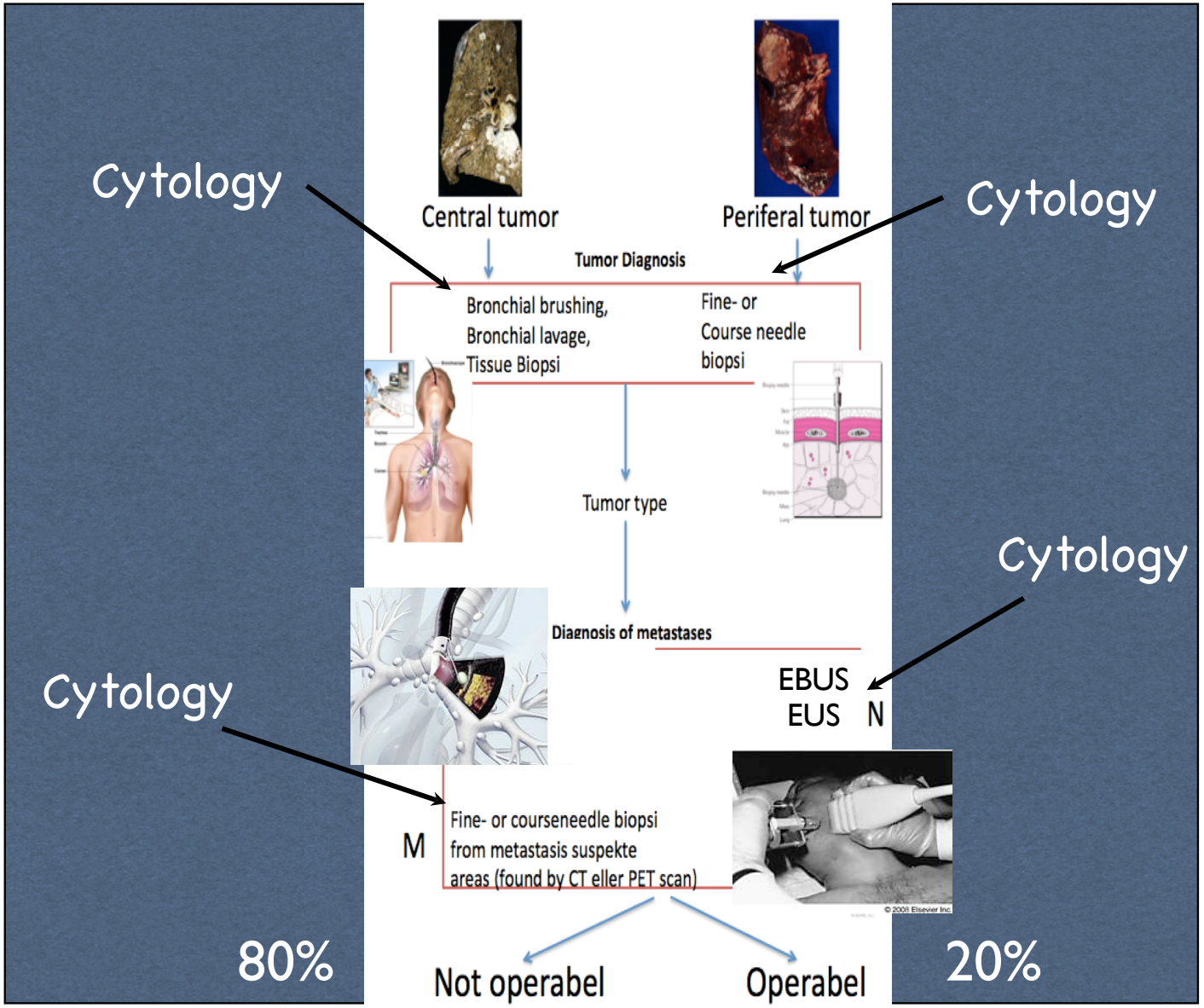
Cancer Therapy: Clinical

Clinical Cancer Research

Agreement between Programmed Cell Death Ligand-1 Diagnostic Assays across Multiple Protein Expression Cutoffs in Non–Small Cell Lung Cancer

Marianne J. Ratcliffe[1], Alan Sharpe[2], Anita Midha[1], Craig Barker[2], Marietta Scott[2], Paul Scorer[2], Hytham Al-Masri[3], Marlon C. Rebelatto[4], and Jill Walker[2]


Cytology
Central tumor
Periferal tumor
Cytology
Tumor Diagnosis
Bronchial brushing,
Bronchial lavage,
Tissue Biopsi
Fine- or
Course needle
biopsi
Tumor type
Cytology
Diagnosis of metastases
EBUS
EUS
N
Cytology
M
Fine- or courseneedle biopsi
from metastasis suspekte
areas (found by CT eller PET scan)
© 2008 Elsevier Inc.
80%
Not operabel
Operabel
20%

Research Article

Paired Comparison of PD-L1 Expression on Cytologic and Histologic Specimens From Malignancies in the Lung Assessed With PD-L1 IHC 28-8pharmDx and PD-L1 IHC 22C3pharmDx

Birgit G. Skov, MD, DrMedSci and Torsten Skov, MD, PhD†*

Conclusion: PD-L1 assessment is feasible on cytologic material with the tested assays using cutoffs for positivity similar to those used on histologic material.

TABLE 3. IHC Staining Outcome in Cytology Samples Compared With Histologic Samples by Agreement Statistics for Different Thresholds of PD-L1 Positivity

	Cutoff ≥ 1% Positive Cells		Cutoff ≥ 50% Positive Cells
PD-L1 IHC 22C3pharmDx			
Overall agreement	85 (76-91)		94 (87-98)
Positive percent agreement	80 (70-87)		100 (96-100)
Negative percent agreement	89 (81-94)		93 (86-97)
	Cutoff ≥ 1% positive cells	Cutoff ≥ 5% positive cells	Cutoff ≥ 10 % positive cells
PD-L1 IHC 28-8 pharmDx			
Overall agreement	87 (79-93)	95 (89-98)	90 (81-94)
Positive percent agreement	81 (72-88)	91 (83-95)	79 (70-87)
Negative percent agreement	93 (86-97)	98 (93-100)	95 (88-98)

Values are represented as percent, 95% CI.
CI indicates confidence interval; IHC, immunohistochemistry; PD-L1, programmed cell death ligand-1.

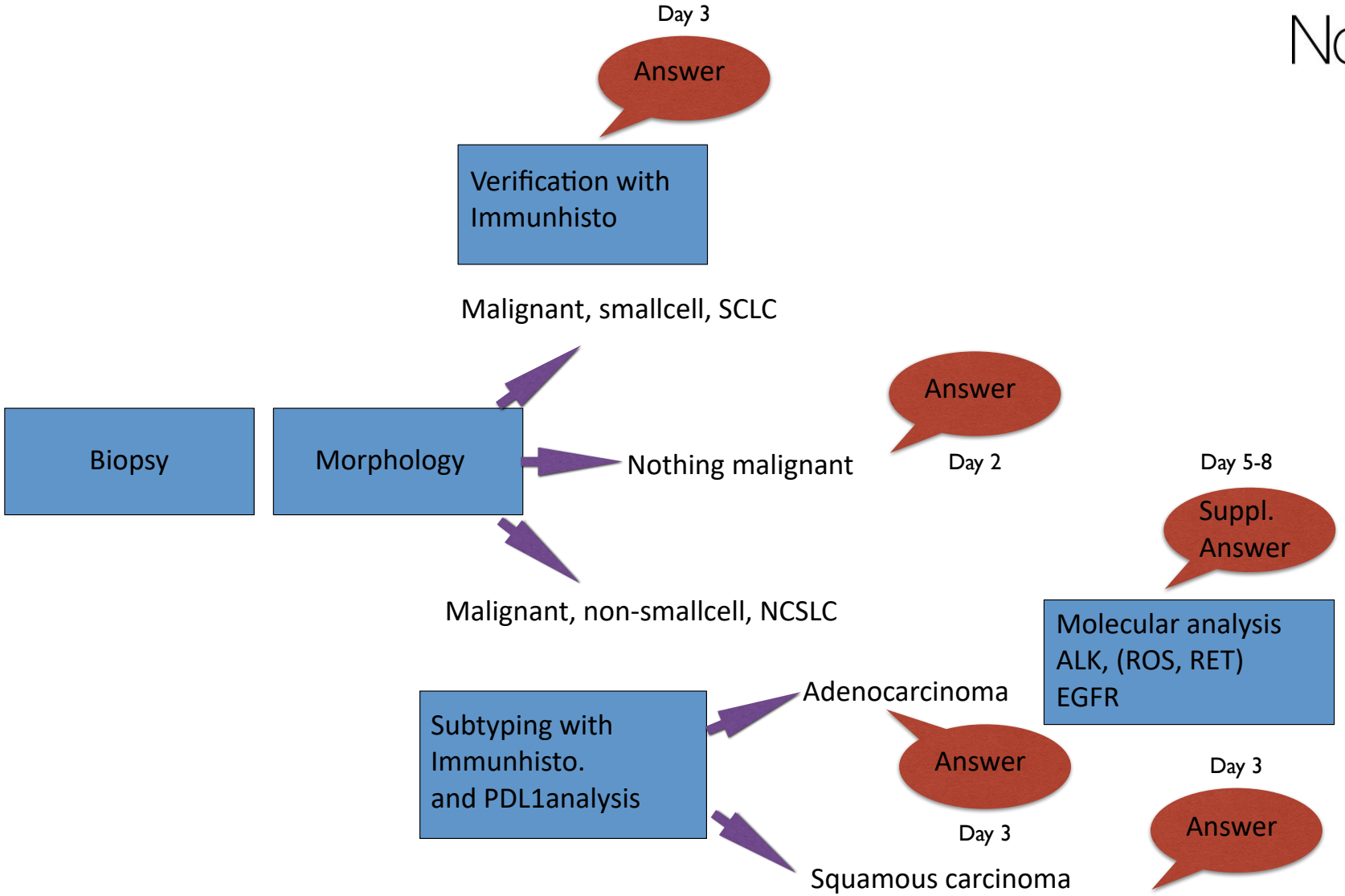
Table 2. **Assessment marks for IHC assays and antibodies run C13, PD-L1 TPS/CPS (KEYTRUDA®)**

CE-IVD / FDA approved PD-L1 assays	n	Vendor	Optimal	Good	Borderline	Poor	Suff.[1]	OR[2]
rmAb clone SP263, **741-4905 (VRPS)[3]**	41	Ventana/Roche	5	33	3	-	93%	12%
rmAb clone SP263, **741-4905 (LPMS)[4]**	2	Ventana/Roche	-	1	1	-	-	-
rmAb clone SP263, **740-4907 (VRPS)[3]**	12	Ventana/Roche	3	9	-	-	100%	25%
mAb clone 22C3 pharmDX, **SK006 (VRPS)[3]**	19	Dako/Agilent	14	4	-	1	95%	74%
mAb clone 22C3 pharmDX, **SK006 (LMPS)[4]**	20	Dako/Agilent	13	5	2	-	90%	65%
mAb clone 22C3 pharmDX, **GE006 (VRPS)[3]**	29	Dako/Agilent	23	6	-	-	100%	79%
mAb clone 22C3 pharmDX, **GE006 (LMPS)[4]**	18	Dako/Agilent	12	4	2	-	89%	67%
rmAb clone 28-8 pharmDX, **SK005 (VRPS)[3]**	3	Dako/Agilent	2	1	-	-	-	-
Antibodies[5] for laboratory developed PD-L1 assays, concentrated antibodies	n	Vendor	Optimal	Good	Borderline	Poor	Suff.[1]	OR[2]
mAb clone **22C3**	44	Dako/Agilent	18	19	7	-	84%	41%
rmAb **CAL10**	4 1	Zytomed Systems Biocare Medical	2	2	-	1	80%	40%
rmAb clone **E1L3N**	4	Cell Signaling	1	3	-	-	-	-
rmAb clone **QR1**	2	Quartett	2	-	-	-	-	-
rmAb clone **28-8**	1	Dako/Agilent	-	1	-	-	-	-
rmAb clone **ZR3**	1	Zeta Corporation	-	1	-	-	-	-
rmAB clone **SP142**	1	Abcam	1	-	-	-	-	-
Ready-To-Use antibodies[6]	n	Vendor	Optimal	Good	Borderline	Poor	Suff.[1]	OR[2]
rmAb clone SP263, **790-4905[6] (VRPS)[3]**	13	Ventana/Roche	-	11	2	-	85%	-
rmAb clone SP263, **790-4905[6] (LMPS)[4]**	16	Ventana/Roche	1	15	-	-	100%	6%
rmAb clone 73-10 **PA0832**	6	Leica Biosystems	5	1	-	-	100%	83%
rmAb MX070C **MAB-0854**	2	Fuzhou Maixin	1	1	-	-	-	-
mAb clone C9C9 **CPM-0278**	1	Celnovte	-	1	-	-	-	-
rmAb clone AC37 **AD80167**	1	Abcarta	1	-	-	-	-	-
rmAb clone RM320 **8263-C010**	1	Sakura Finetek	1	-	-	-	-	-
rmAb clone BP6099 **I12052E**	1	Biolynx	1	-	-	-	-	-
Total	243		106	118	17	2		
Proportion			44%	48%	7%	1%	92%	

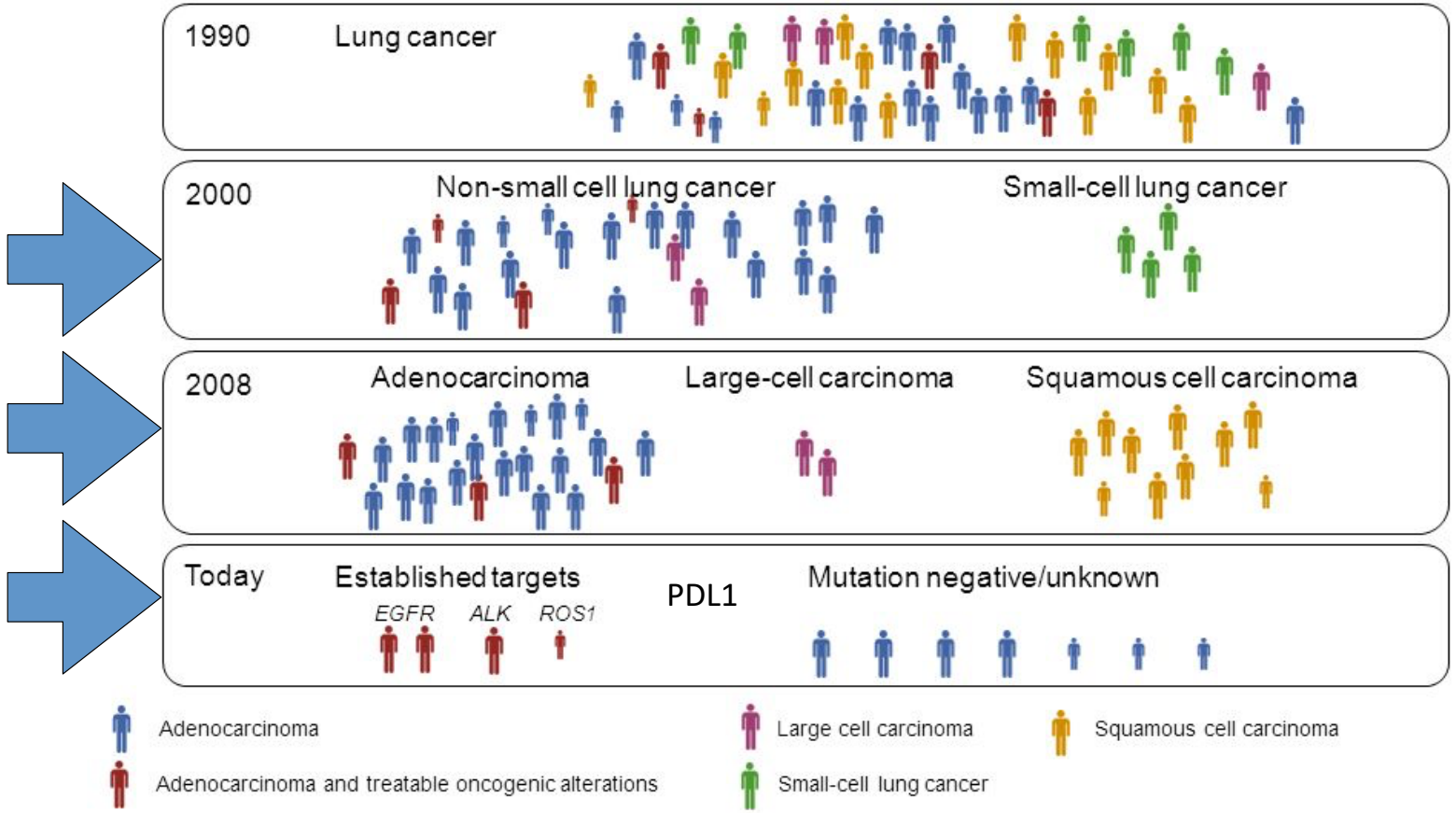
1) Proportion of sufficient stains (optimal or good).
2) Proportion of optimal results.
3) Vendor recommended protocol settings – RTU product used in compliance to protocol settings, platform and package insert.
4) Laboratory modified protocol settings for a RTU product applied either on the vendor recommended platform(s) or other platforms.
5) mAb: mouse monoclonal antibody, rmAb: rabbit monoclonal antibody.
6) Ready-To-Use antibodies without predictive claim.

The Diagnostic algorithm

The Diagnostic algorithm

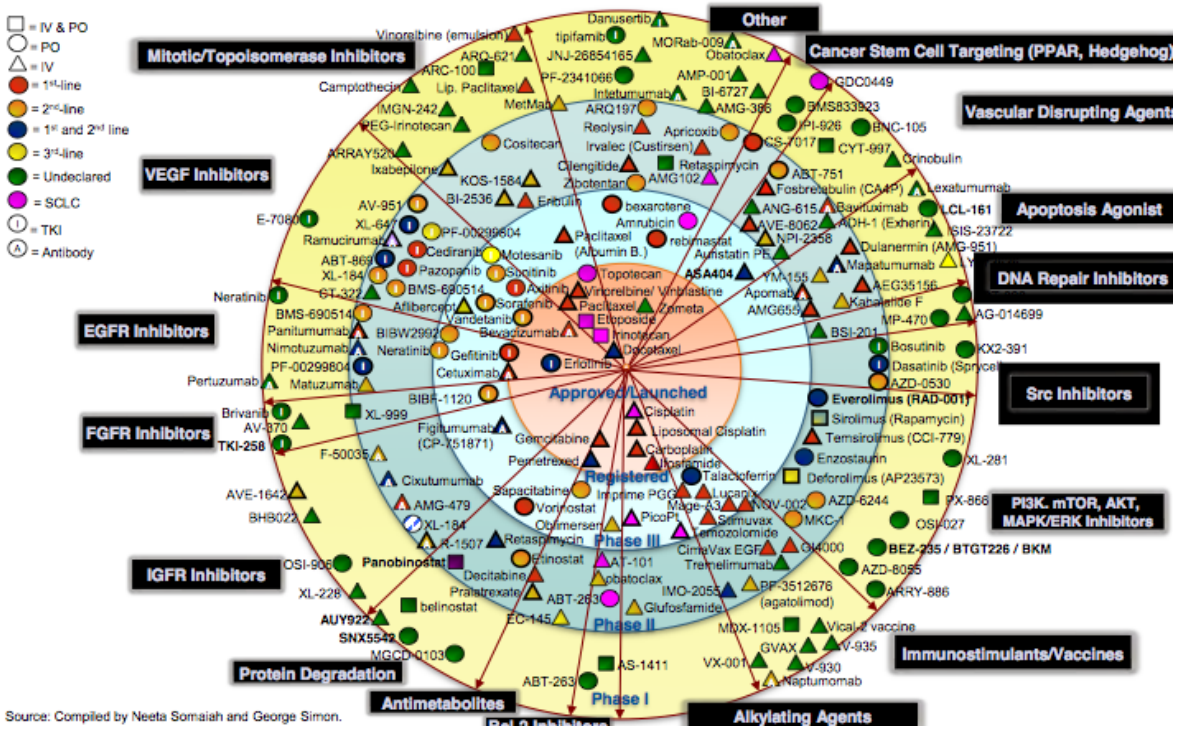


Patient selection in lung cancer: Evolution over time



Adapted from Reck M, et al. Lancet 2013;382:709–19

Lung cancer research landscape – MoA group and phase



Future