Immunomarkers for Characterization of Oligometastatic Disease: Role for Diagnosis and Treatment

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Commentary

Who are appropriate surgical candidates among patients with oligometastatic non-small cell lung cancer?

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Provenance: This is an invited Commentary commissioned by the Editorial Board Member Yoshihisa Shimada (Department of Thoracic Surgery, Tokyo Medical University, Nishishinjuku, Shinjuku-ku, Tokyo, Japan).

Comment on: Johnson KK, Rosen JE, Salazar MC, *et al*. Outcomes of a Highly Selective Surgical Approach to Oligometastatic Lung Cancer. Ann Thorac Surg 2016;102:1166-71.

Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: a multicentre, randomised, controlled, phase 2 study

Daniel R Gomez, George R Blumenschein Jr, J Jack Lee, Mike Hernandez, Rong Ye, D Ross Camidge, Robert C Doebele, Ferdinandos Skoulidis, Laurie E Gaspar, Don L Gibbons, Jose A Karam, Brian D Kavanagh, Chad Tang, Ritsuko Komaki, Alexander V Louie, David A Palma, Anne S Tsao, Boris Sepesi, William N William, Jianjun Zhang, Qiuling Shi, Xin Shelley Wang, Stephen G Swisher, John V Heymach**

Lancet Oncol 2016; 17: 1672–82

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Summary

Background Evidence from retrospective studies suggests that disease progression after first-line chemotherapy for metastatic non-small-cell lung cancer (NSCLC) occurs most often at sites of disease known to exist at baseline. However, the potential effect of aggressive local consolidative therapy for patients with oligometastatic NSCLC is unknown. We aimed to assess the effect of local consolidative therapy on progression-free survival.

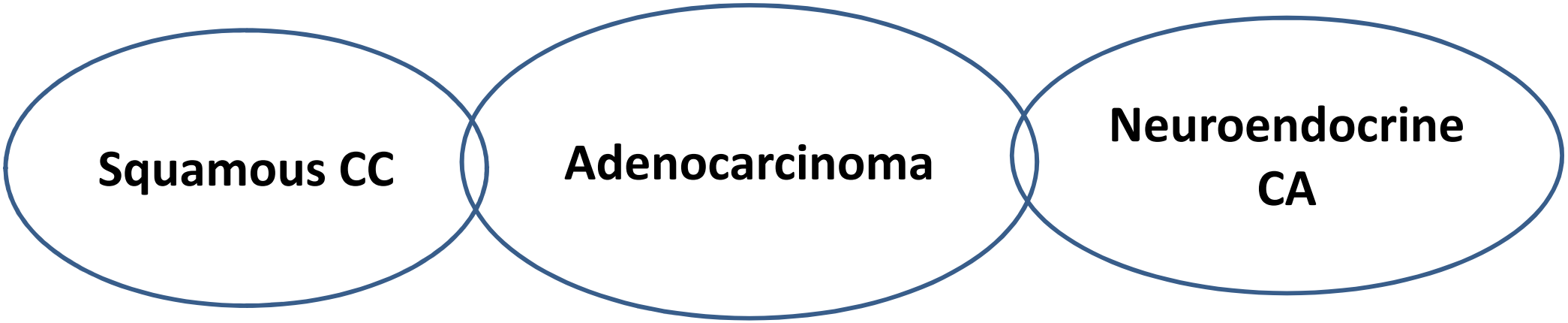
What is Oligometastatic Disease?

- Essentially a Stage IV disease
- Systemic chemotherapy (or in the near future immunotherapy) in theory would be the first-line treatment
- Phase II study recently suggested exploring aggressive local therapy in context of a Phase III study

What is Oligometastatic Disease?

- Definition of oligometastatic status impacts over diagnostic workflow
- Biopsy vs surgical specimen
- Post-treatment specimen
- Isolated metastases (brain or adrenal) raise the question of a (rare) second primary

Lung Cancer



Heterogeneous disease

Several therapeutic implications

WHO histological classification of tumours of the lung

Malignant epithelial tumours

Squamous cell carcinoma	8070/3
Papillary	8052/3
Clear cell	8084/3
Small cell	8070/3
Basaloid	8083/3
Small cell carcinoma	8041/3
Combined small cell carcinoma	8045/3
Adenocarcinoma	8140/3
Adenocarcinoma, mixed subtype	8255/3
Acinar adenocarcinoma	8551/3
Papillary adenocarcinoma	8260/3
Bronchioloalveolar carcinoma	8250/3
Nonmucinous	8252/3
Mucinous	8253/3
Mixed nonmucinous and mucinous or indeterminate	8254/3
Solid adenocarcinoma with mucin production	8230/3
Fetal adenocarcinoma	8333/3
Mucinous ("colloid") carcinoma	8480/3
Mucinous cystadenocarcinoma	8470/3
Signet ring adenocarcinoma	8490/3
Clear cell adenocarcinoma	8310/3
Large cell carcinoma	8012/3
Large cell neuroendocrine carcinoma	8013/3
Combined large cell neuroendocrine carcinoma	8013/3
Basaloid carcinoma	8123/3
Lymphoepithelioma-like carcinoma	8082/3
Clear cell carcinoma	8310/3
Large cell carcinoma with rhabdoid phenotype	8014/3
Adenosquamous carcinoma	8560/3
Sarcomatoid carcinoma	8033/3
Pleomorphic carcinoma	8022/3
Spindle cell carcinoma	8032/3
Giant cell carcinoma	8031/3
Carcinosarcoma	8980/3
Pulmonary blastoma	8972/3
Carcinoid tumour	8240/3
Typical carcinoid	8240/3
Atypical carcinoid	8249/3
Salivary gland tumours	
Mucoepidermoid carcinoma	8430/3
Adenoid cystic carcinoma	8200/3
Epithelial–myoepithelial carcinoma	8562/3
Preinvasive lesions	
Squamous carcinoma *in situ*	8070/2
Atypical adenomatous hyperplasia	
Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia	

Mesenchymal tumours

Epithelioid haemangioendothelioma	9133/1
Angiosarcoma	9120/3
Pleuropulmonary blastoma	8973/3
Chondroma	9220/0
Congenital peribronchial myofibroblastic tumour	8827/1
Diffuse pulmonary lymphangiomatosis	
Inflammatory myofibroblastic tumour	8825/1
Lymphangioleiomyomatosis	9174/1
Synovial sarcoma	9040/3
Monophasic	9041/3
Biphasic	9043/3
Pulmonary artery sarcoma	8800/3
Pulmonary vein sarcoma	8800/3

Benign epithelial tumours

Papillomas	
Squamous cell papilloma	8052/0
Exophytic	8052/0
Inverted	8053/0
Glandular papilloma	8260/0
Mixed squamous cell and glandular papilloma	8560/0
Adenomas	
Alveolar adenoma	8251/0
Papillary adenoma	8260/0
Adenomas of the salivary gland type	
Mucous gland adenoma	8140/0
Pleomorphic adenoma	8940/0
Others	
Mucinous cystadenoma	8470/0

Lymphoproliferative tumours

Marginal zone B-cell lymphoma of the MALT type	9699/3
Diffuse large B-cell lymphoma	9680/3
Lymphomatoid granulomatosis	9766/1
Langerhans cell histiocytosis	9751/1

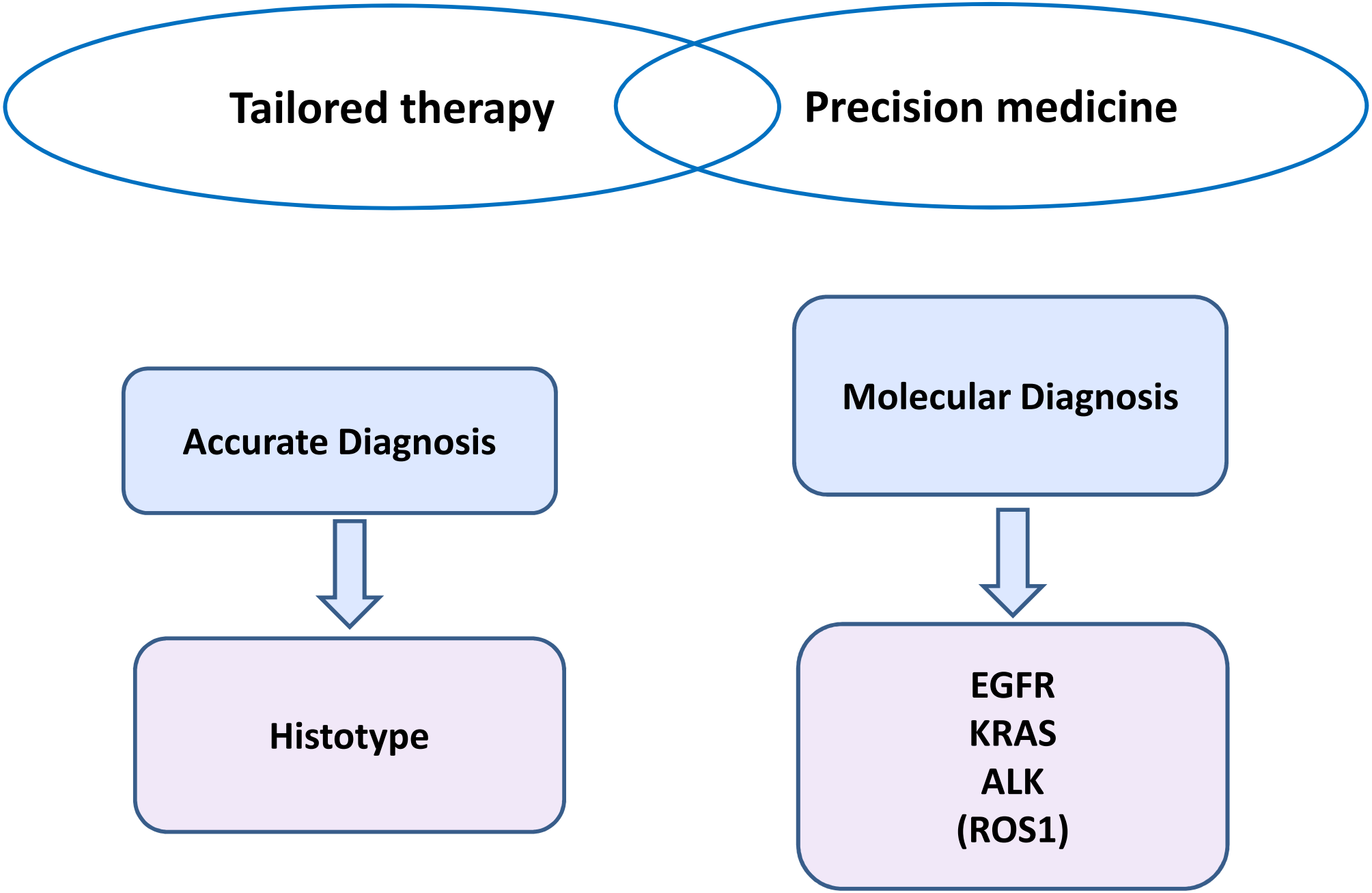
Miscellaneous tumours

Hamartoma	
Sclerosing hemangioma	8832/0
Clear cell tumour	8005/0
Germ cell tumours	
Teratoma, mature	9080/0
Immature	9080/3
Other germ cell tumours	
Intrapulmonary thymoma	8580/1
Melanoma	8720/3

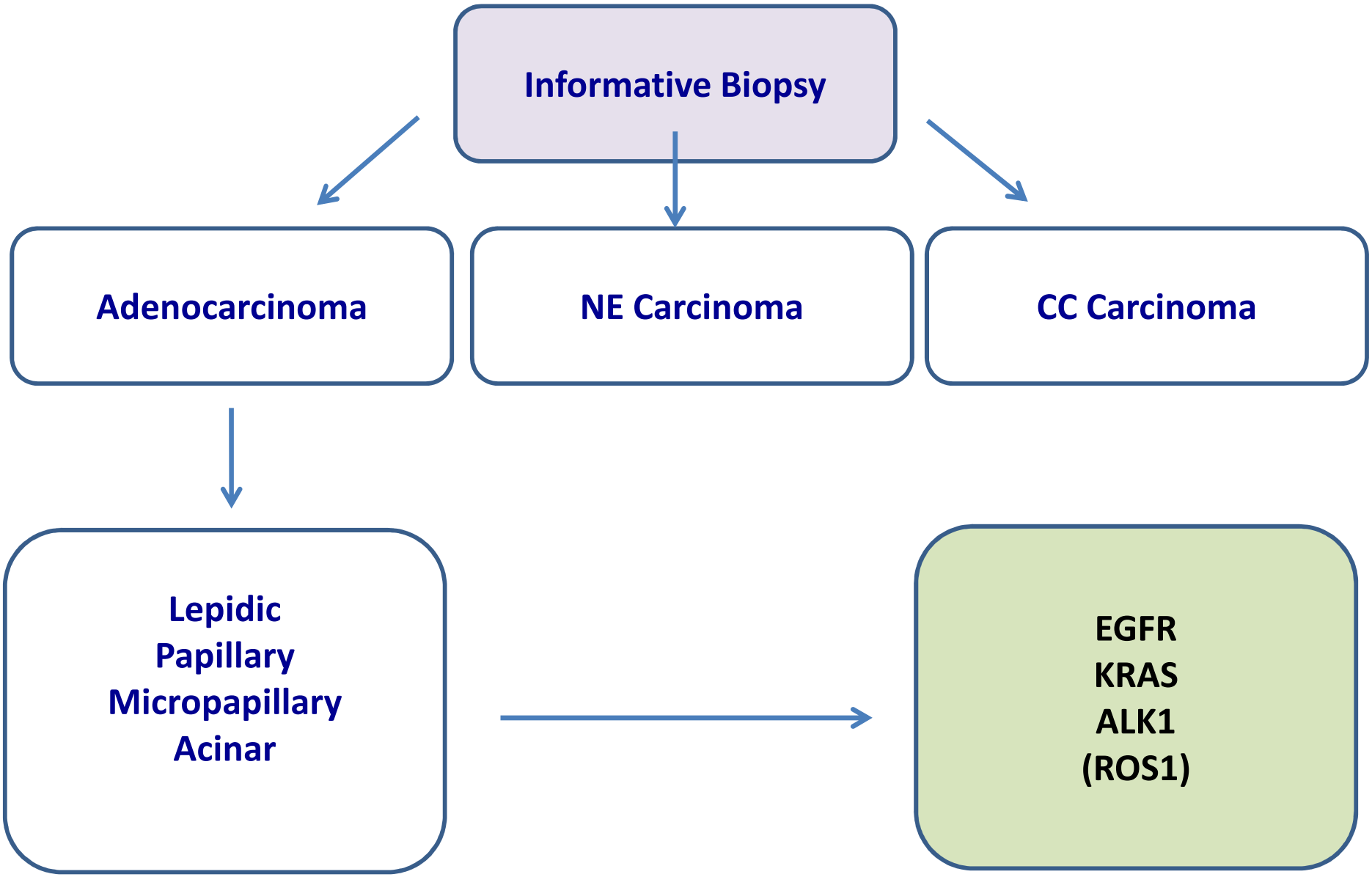
Metastatic tumours

[1] Morphology code of the International Classification of Diseases for Oncology (ICD-O) [8] and the Systematized Nomenclature of Medicine (http://snomed.org). Behaviour is coded /0 for benign tumours, /3 for malignant tumours, and /1 for borderline or uncertain behaviour.

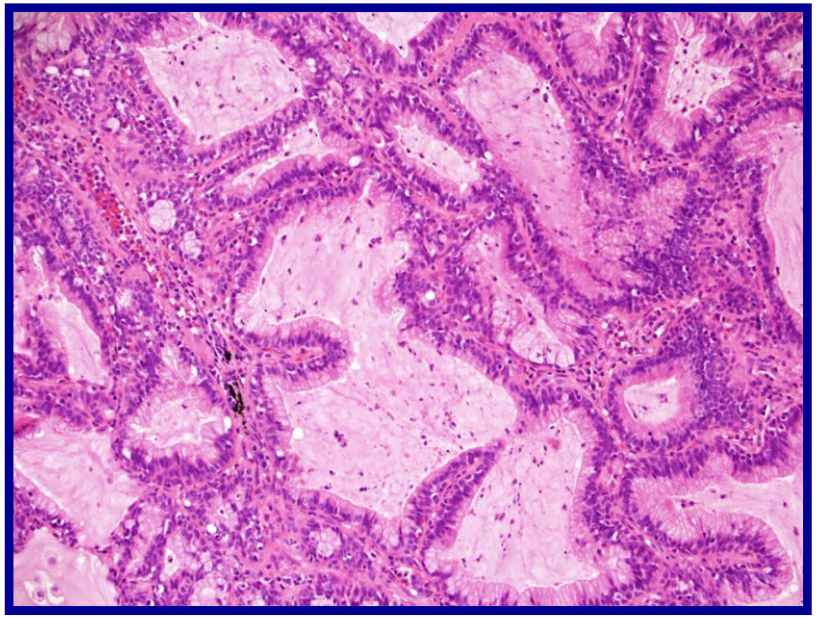
Now WHO classification applicable to bioptic samples

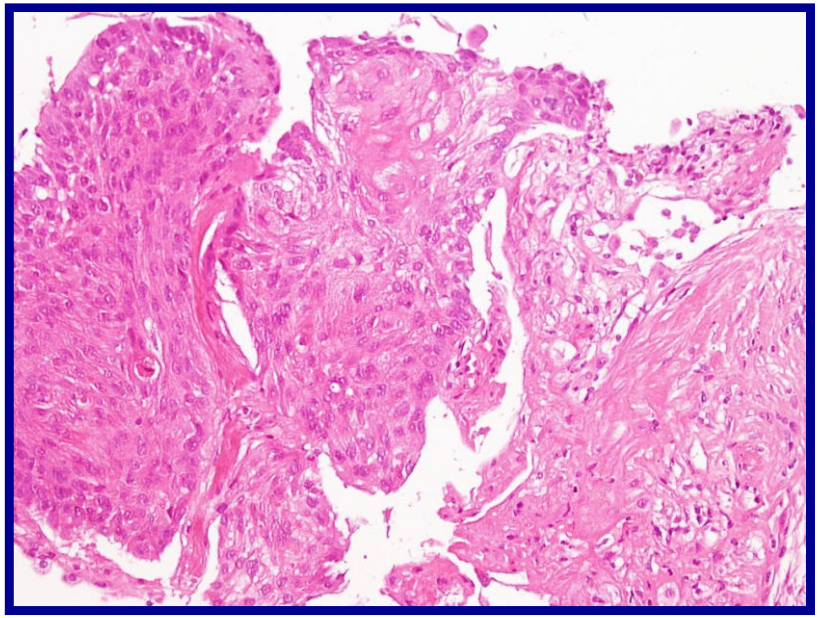

Tailored therapy
Precision medicine
Accurate Diagnosis
Histotype
Molecular Diagnosis
EGFR
KRAS
ALK
(ROS1)

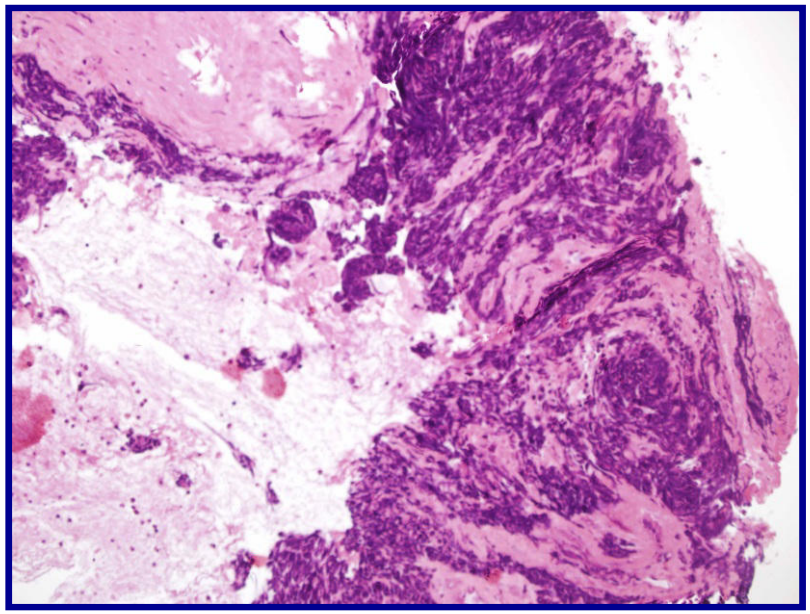
Morphology OK



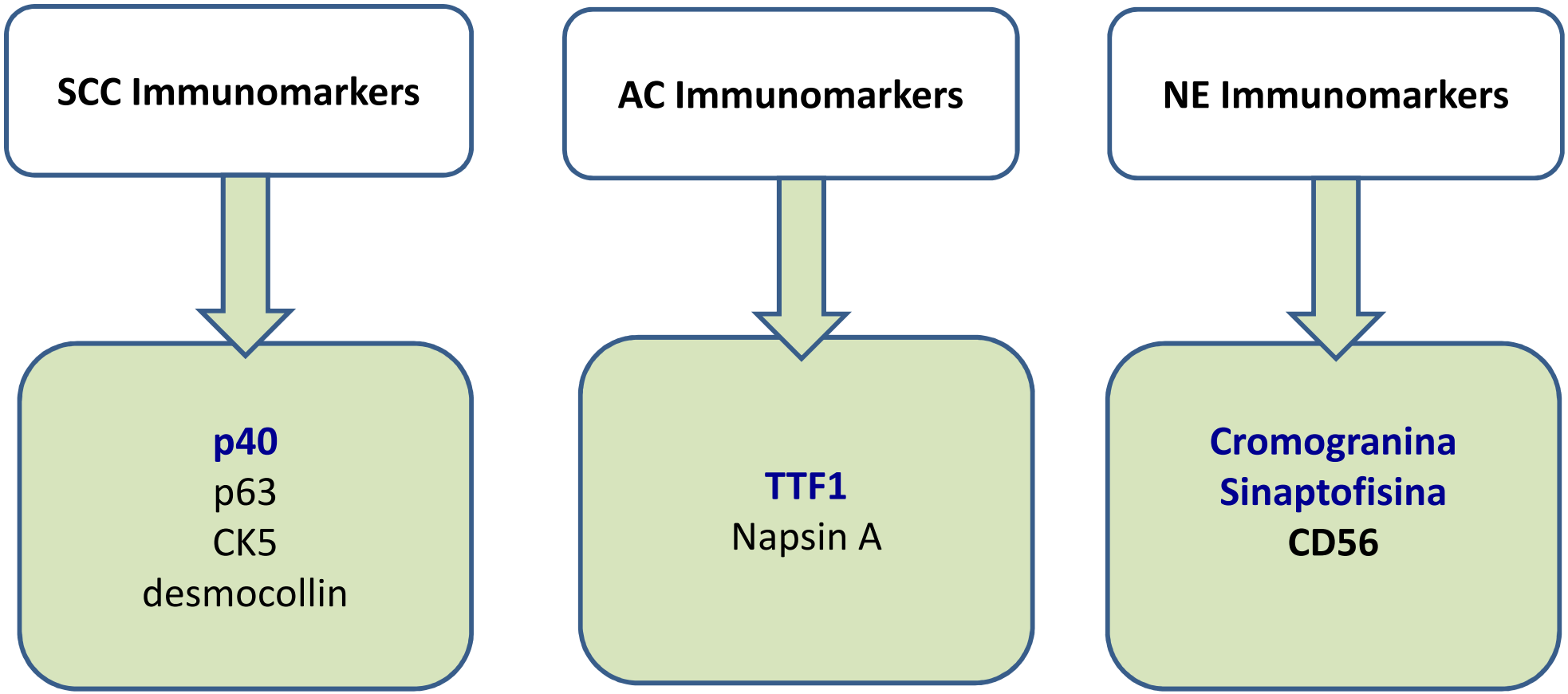
Informative Morphology







Undefined Morphology
Immunophenotype



Various Antibody Clones of Napsin A, Thyroid Transcription Factor 1, and p40 and Comparisons With Cytokeratin 5 and p63 in Histopathologic Diagnostics of Non–Small Cell Lung Carcinoma

Lena Tran, BSc, Johanna S.M. Mattsson, MSc,† Björn Nodin, PhD,‡ Per Jönsson, MD, PhD,§ Maria Planck, MD, PhD,‡‖ Karin Jirström, MD, PhD,*‡ Johan Botling, MD, PhD,† Patrick Micke, MD, PhD,† and Hans Brunnström, MD, PhD*‡*

(*Appl Immunohistochem Mol Morphol* 2016;24:648–659)

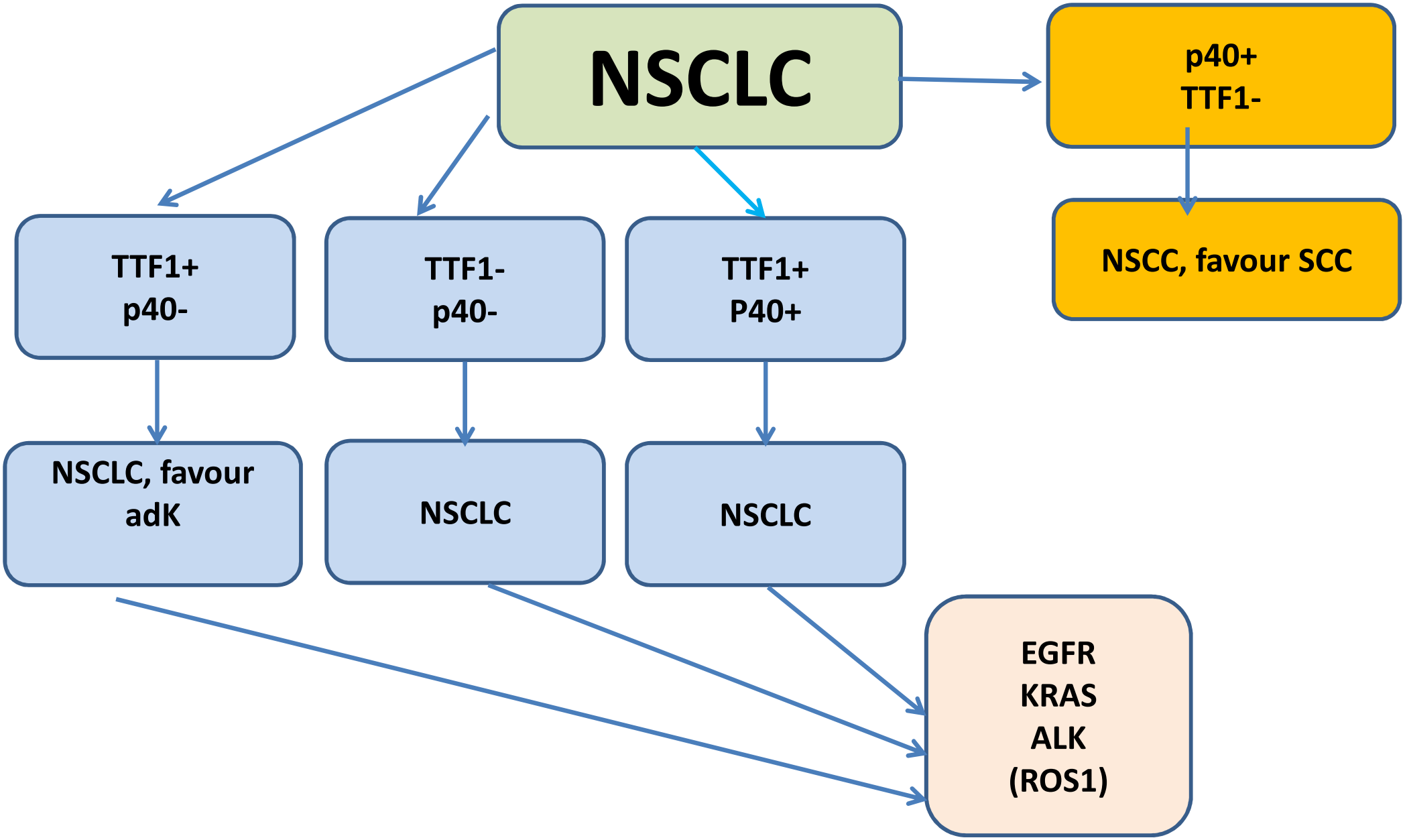
TABLE 2. Frequency of Lung Cancer Cases With at Least 1%/>10% Positive Tumor Cells (Fraction 1+ and 2+, Respectively)

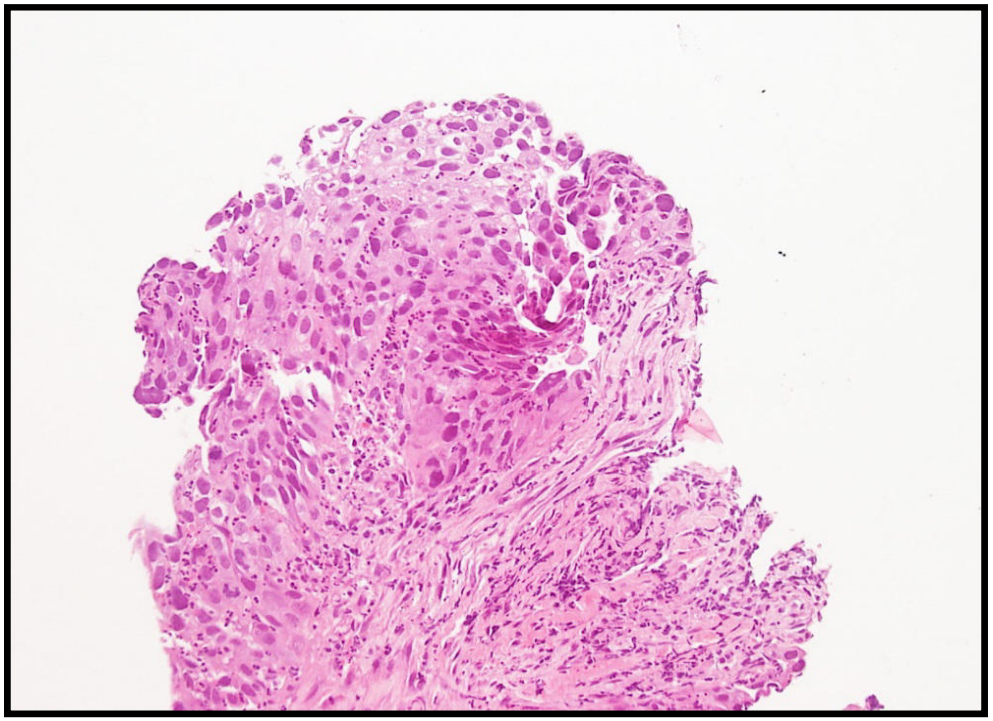
Antibody	Clone	SCC (%)	AC (%)	LCC (%)	LCNEC (%)	ASqC (%)	SC (%)
CK5	XM26	96/95	1/0.3	7/3	6/0	83/75	25/0
p63	4A4	95/95	23/11	21/10	6/0	92/92	50/25
p40	BC28	95/94	2/0.7	7/7	0	90/90	40/0
p40	Polyclonal	95/94	3/0.4	4/4	0	91/91	50/0
NAPA	TMU-Ad02	4/2	88/84	33/33	0	45/45	50/25
NAPA	MRQ60	4/3	87/83	47/47	7/7	44/44	40/20
NAPA	Polyclonal	6/4	90/87	46/46	0	50/40	67/33
NAPA	IP64 1:100	4/2	88/86	30/30	0	45/45	40/20
NAPA	IP64 1:20	5/3	89/87	38/35	6/6	42/42	50/25
TTF-1	8G7G3/1	3/3	89/85	50/47	72/61	50/42	40/20
TTF-1	SPT24	7/5	93/90	50/50	83/78	67/42	40/40

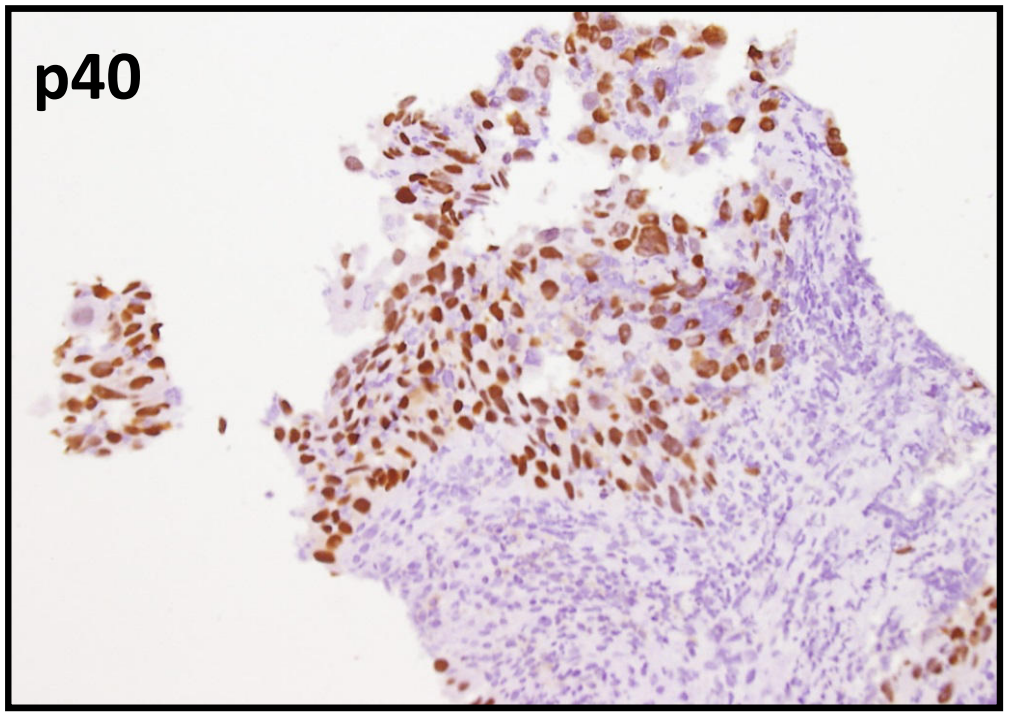
Note that NAPA-positive LCNEC is a combined tumor (see text for details).

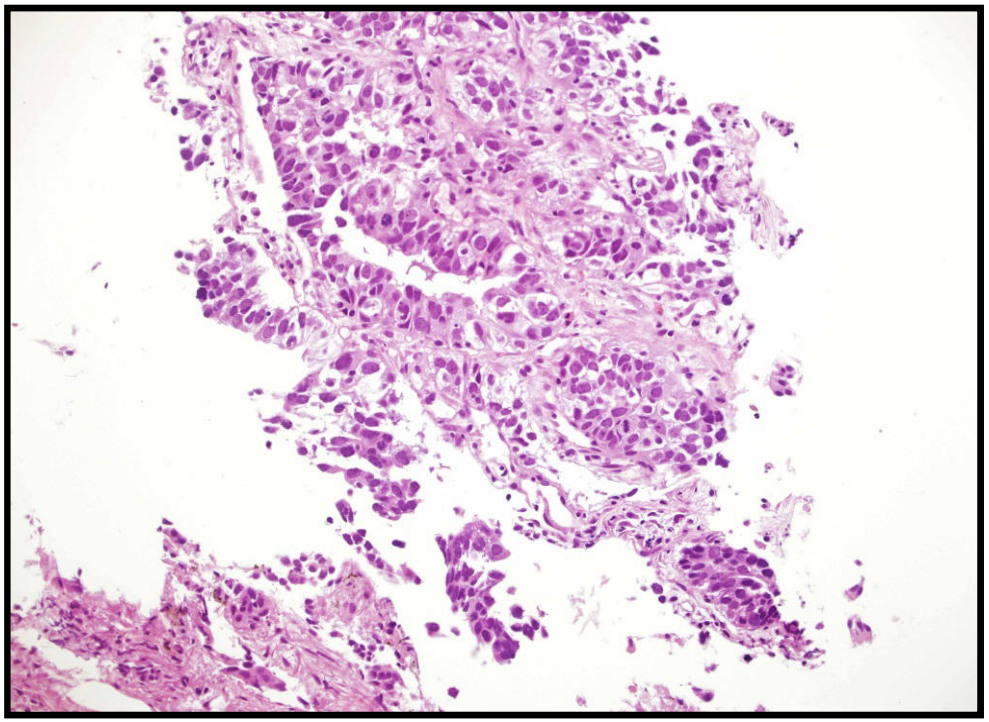
AC indicates adenocarcinoma; ASqC, adenosquamous carcinoma; CK, cytokeratin; LCC, large cell carcinoma; LCNEC, large cell neuroendocrine carcinoma; NAPA, napsin A; SC, sarcomatoid carcinoma; SCC, squamous cell carcinoma; TTF-1, thyroid transcription factor 1.

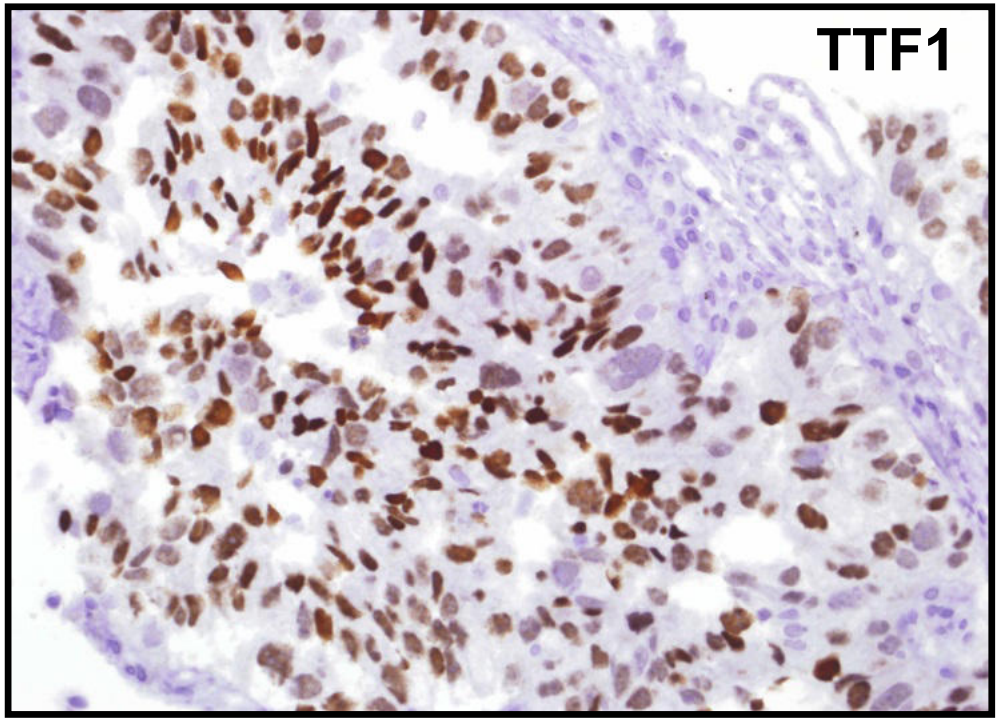
NSCLC: AC vs SCC






p40

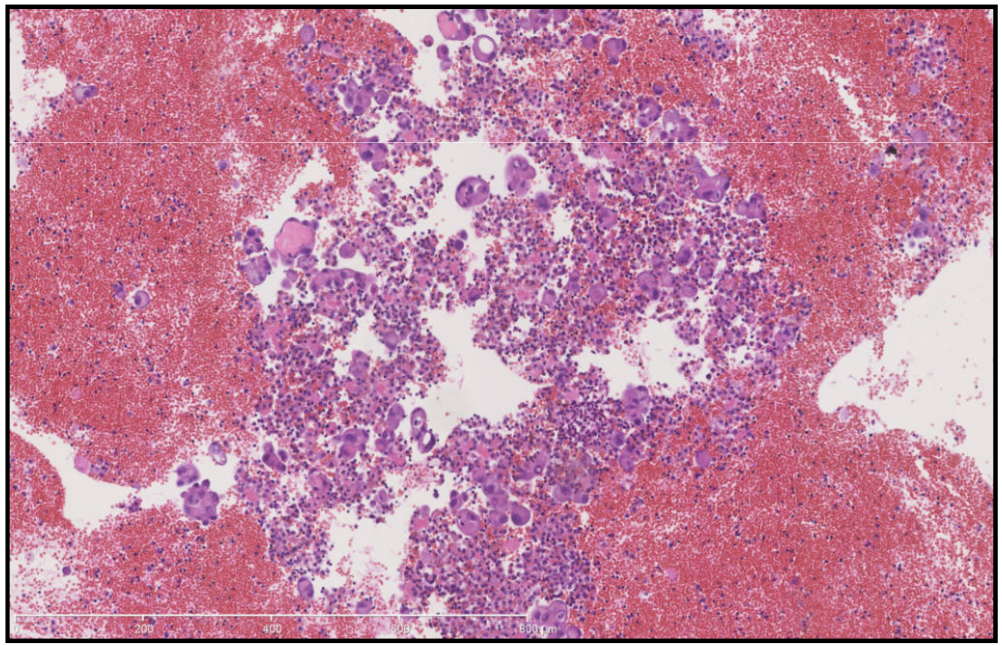


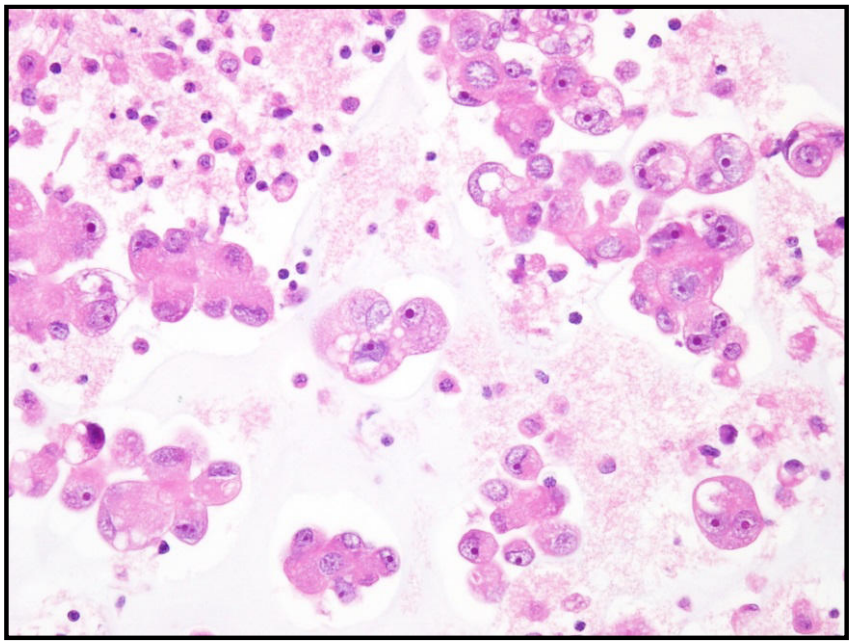

TTF1

Cell Block

- From cytologic sample (EBUS-TBNA)
- From pleural effusion

IHC OK – Molecular Testing OK





EBUS-TBNA (Endobronchial Ultrasound-guided transBronchial Needle Aspiration)

- Minimally invasive procedure
- As safe as bronchoscopy
- Less invasive than mediastinoscopy

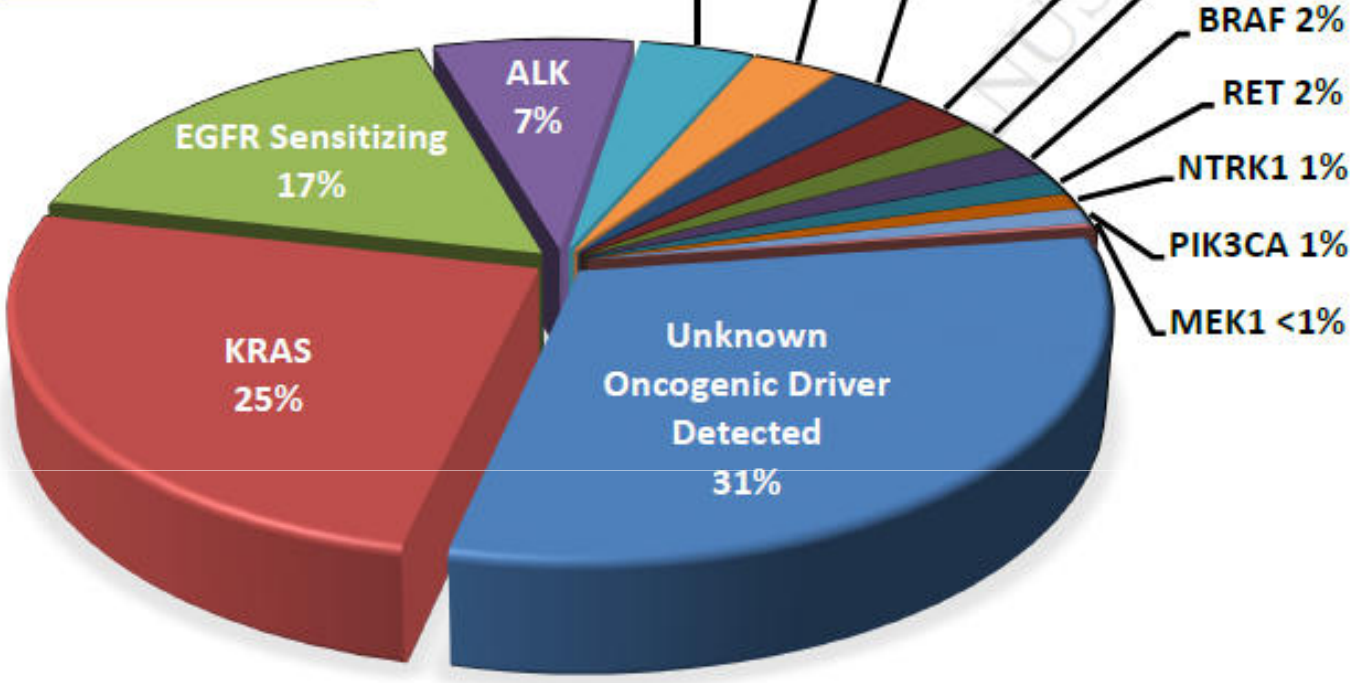
	EBUS-TBNA			SURGICAL SERIE			p-value*
	N	MUT/REARR.	WT	N	MUT/REARR	WT	
EGFR	189	32 (16.9%)	157 (83.1%)	1000	148 (14.8%)	852 (85.2%)	0.45
KRAS	136	43 (31.6%)	93 (68.4%)	1000	290 (29%)	710 (71%)	0.53
ALK .	152	6 (3.9%)	146 (96.1%)	1000	34 (3.4%)	966 (96.6%)	0.73

*Chi-square test

Legend: MUT/REARR : mutated/rearranged; WT: wild type; N : number of cases .

Am J Clin Pathol 2015

Adenocarcinoma



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]

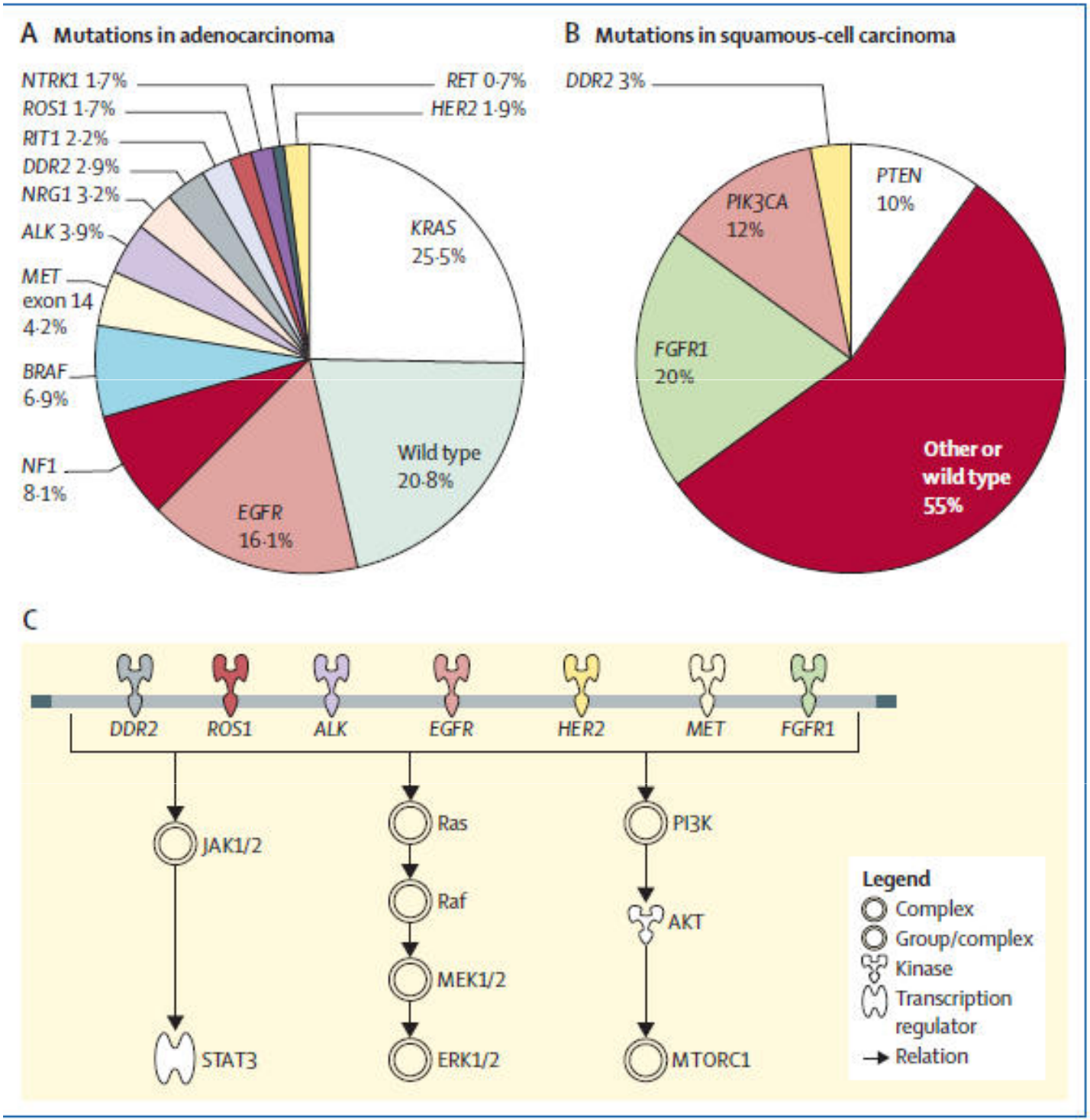
NTRK1
- Entrectinib [2]
- LOXO-101 [2]
- Cabozantinib [2]
- DS-6051b [1]

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



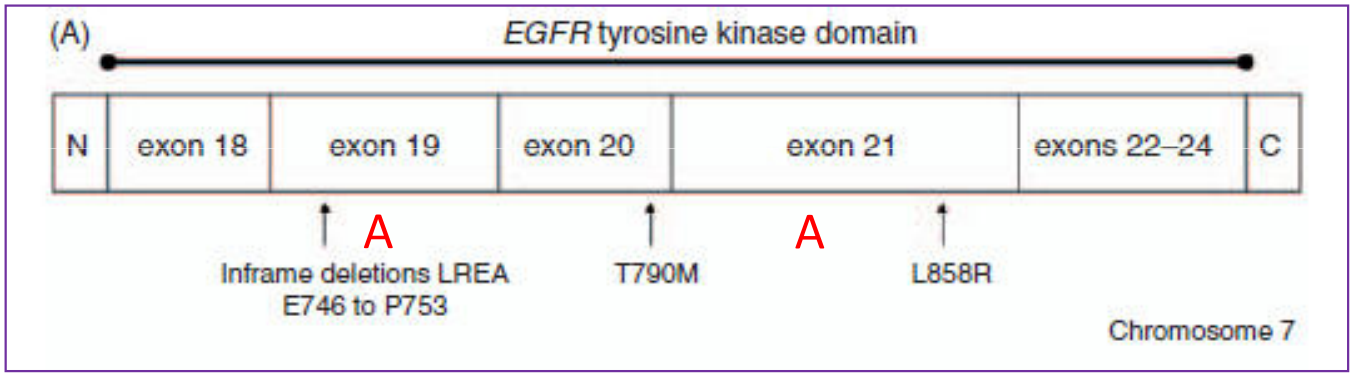
Rosell & Karachaliou 2016

EGFR

Table 1 *EGFR* Mutations

Type	Mutation	Population Primarily Affected	Clinical Implication For Anti-EGFR–TKI Therapy
Activating	Exon 19 del	Anti-EGFR–TKI-naive patients	Confers sensitivity
Activating	L858R 21	Anti-EGFR–TKI-naive patients	Confers sensitivity
Resistance	T790M 20	Anti-EGFR–TKI-treated patients	Confers resistance
Resistance	Exon 20	Anti-EGFR–TKI-naive patients	Confers resistance

EGFR = epidermal growth factor receptor; Exon 19 del = deletion in exon 19; L858R = leucine-to-arginine substitution at position 858; T790M = threonine-to-methionine amino acid change at position 790; TKI = tyrosine kinase inhibitor.



Activating mutations represents up to 90% of EGFR mutated cases

mEGFR When?

- Adenocarcinoma
- NSLCC, NAS
- adenosquamous

mEGFR Where?

- Surgical specimen (primary or metastasis)
- Biopsy (primary or metastasis)
- Citology (primary or metastasis)

The International Association for the Study of Lung Cancer Consensus Statement on Optimizing Management of *EGFR* Mutation–Positive Non–Small Cell Lung Cancer: Status in 2016

Daniel S. W. Tan, M.B.B.S., MRCP,[a] Sue S. Yom, MD, PhD,[b] Ming S. Tsao, MD, FRCPC,[c] Harvey I. Pass, MD,[d] Karen Kelly, MD,[e] Nir Peled, MD, PhD,[f] Rex C. Yung, MD,[g] Ignacio I. Wistuba, MD,[h] Yasushi Yatabe, MD, PhD,[i] Michael Unger, MD,[j] Philip C. Mack, PhD,[e] Murry W. Wynes, PhD,[k] Tetsuya Mitsudomi, MD,[l] Walter Weder, MD,[m] David Yankelevitz, MD,[n] Roy S. Herbst, MD, PhD,[o] David R. Gandara, MD,[e] David P. Carbone, MD, PhD,[p] Paul A. Bunn Jr., MD,[q] Tony S. K. Mok, MD,[r,*] Fred R. Hirsch, MD, PhD[q]

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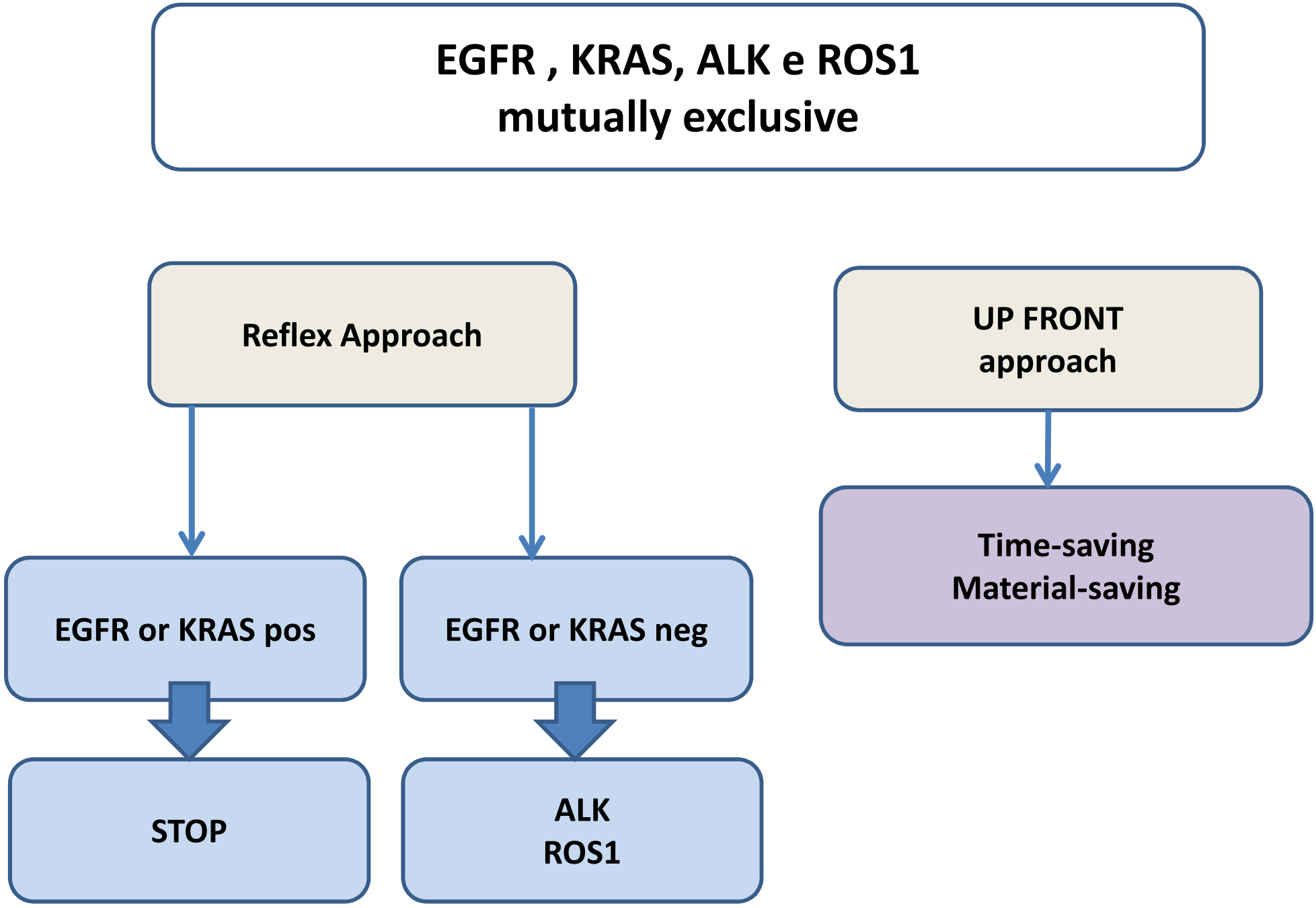
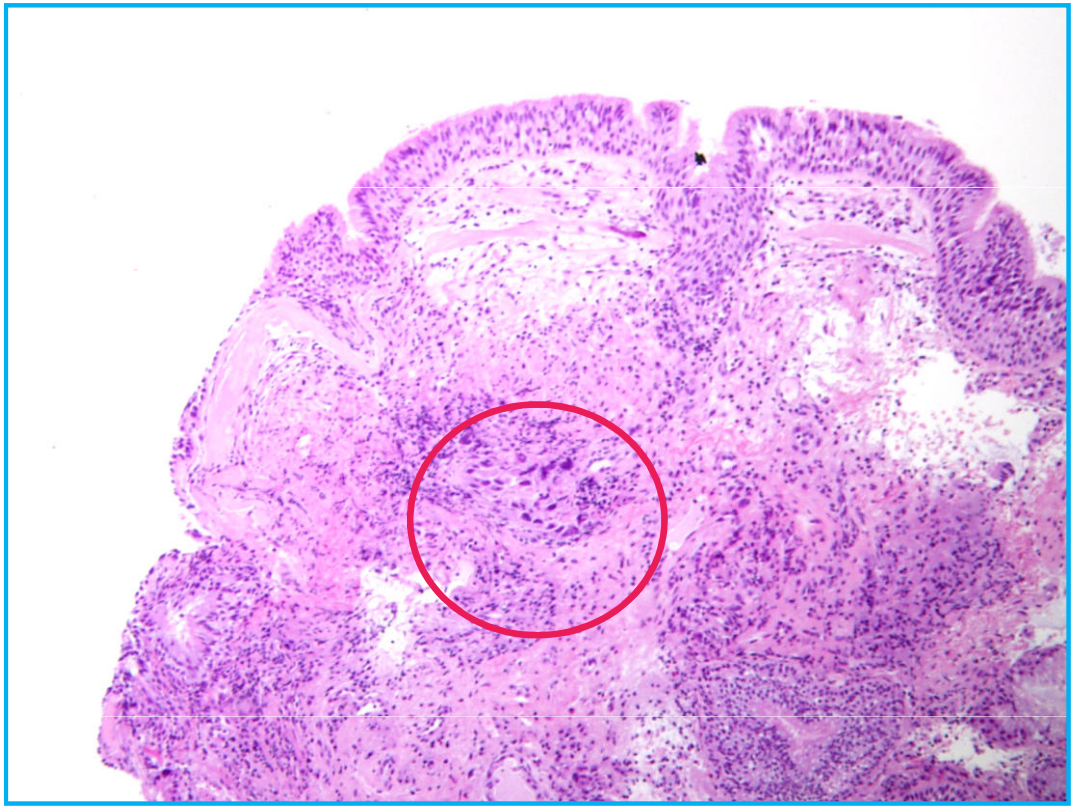

EGFR , KRAS, ALK e ROS1
mutually exclusive
Reflex Approach
EGFR or KRAS pos
EGFR or KRAS neg
STOP
ALK
ROS1
UP FRONT
approach
Time-saving
Material-saving

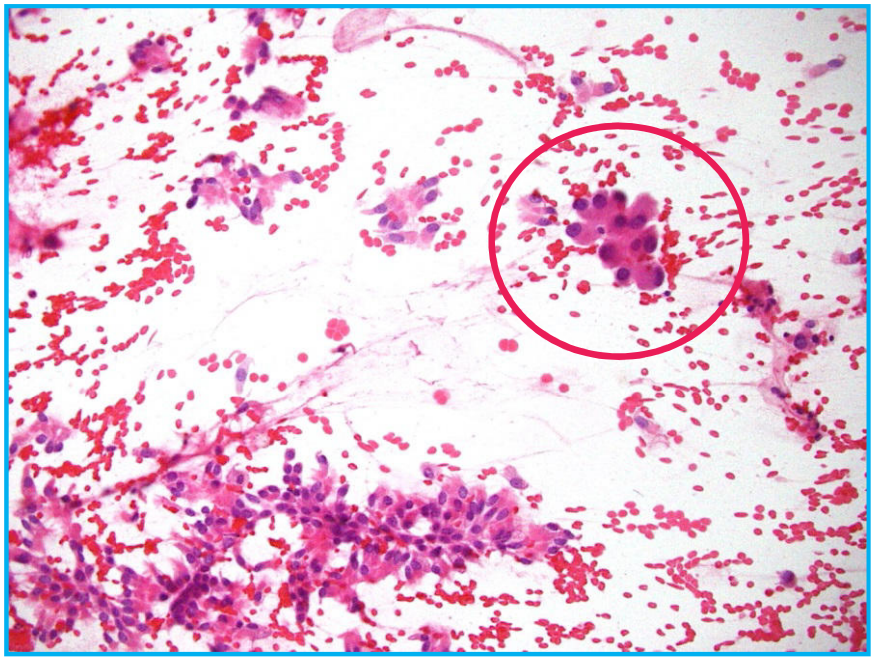
Amount of Material is an Issue IHC/PDL1/EGFR/KRAS/ALK/ROS1

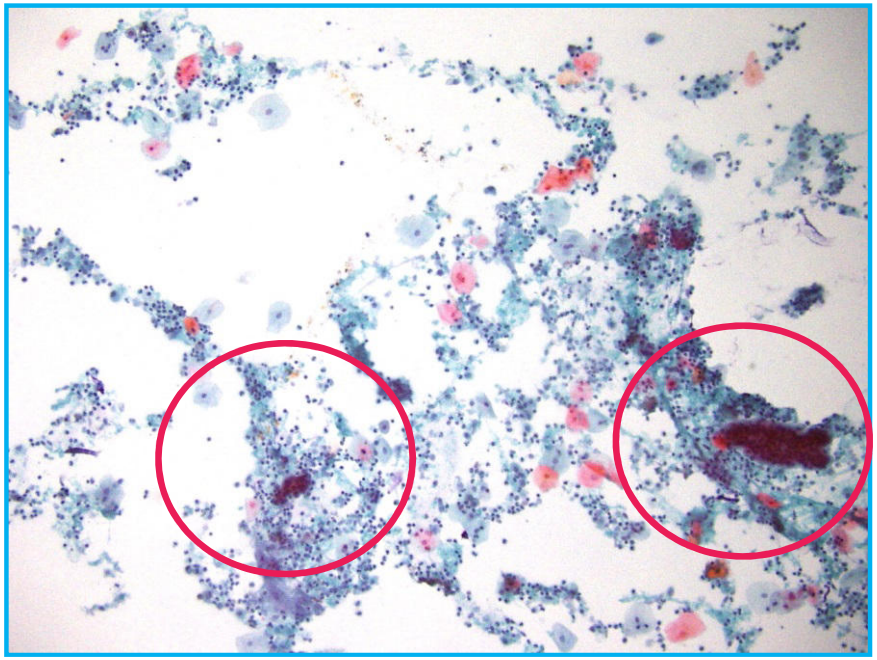
Quantity At least 100 cells

Quality

Inadequate for molecular testing and FISH







Tumor Heterogeneity

- Oligometastatic is metastatic
- Tumor heterogeneity also applies to oligometastatic status
- Impact over therapeutic planning
- Small chance of “second primary”

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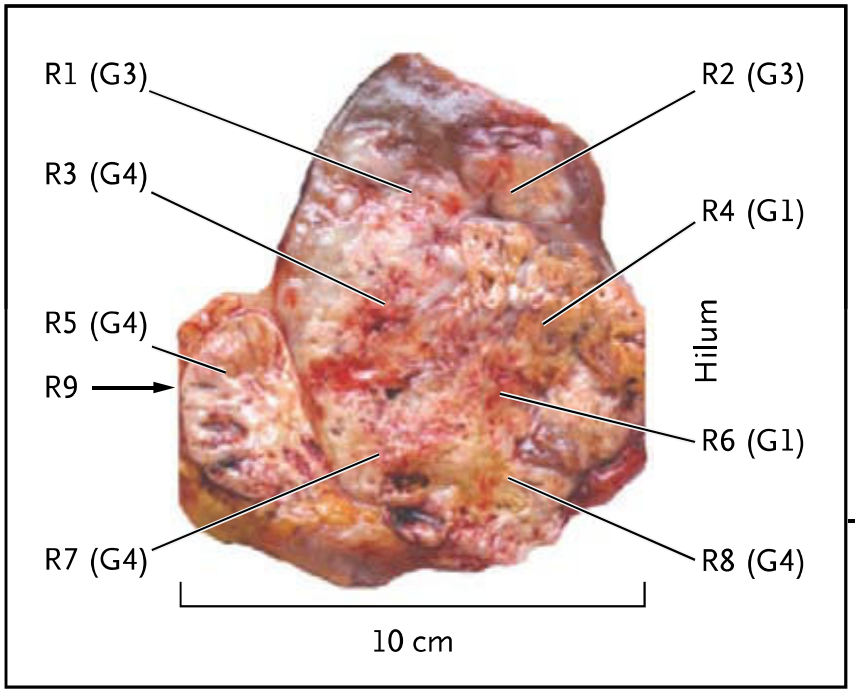
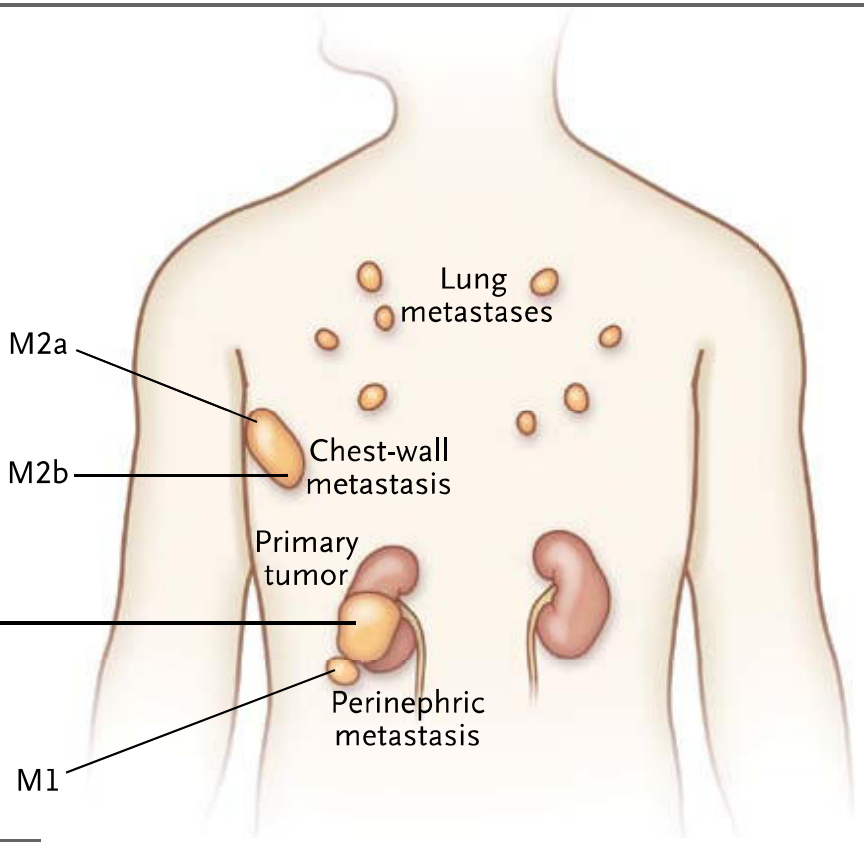
Intratumor Heterogeneity and Branched Evolution Revealed by Multiregion Sequencing

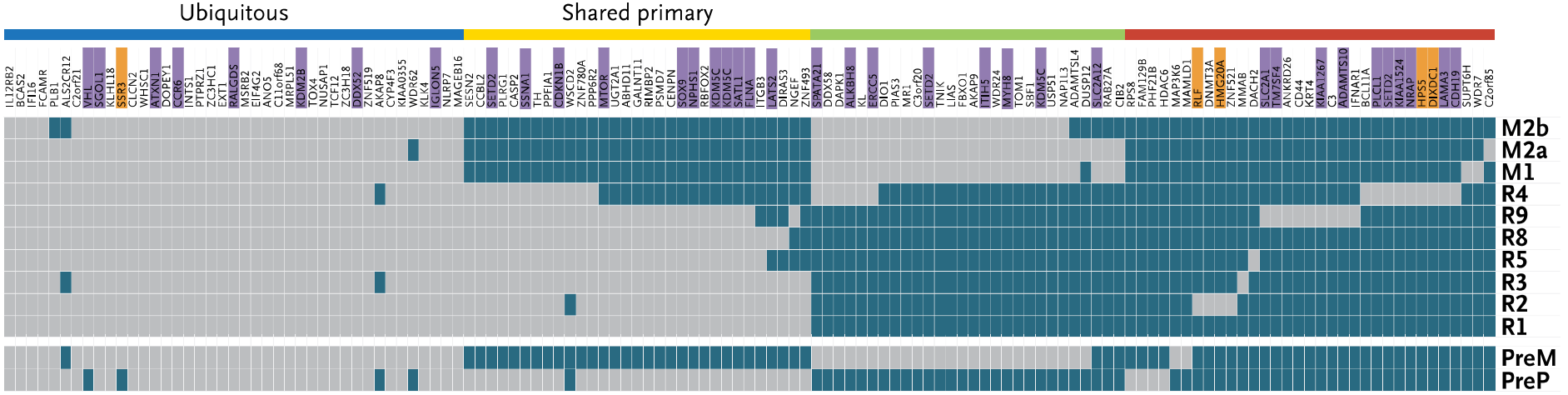
Marco Gerlinger, M.D., Andrew J. Rowan, B.Sc., Stuart Horswell, M.Math., James Larkin, M.D., Ph.D., David Endesfelder, Dip.Math., Eva Gronroos, Ph.D., Pierre Martinez, Ph.D., Nicholas Matthews, B.Sc., Aengus Stewart, M.Sc., Patrick Tarpey, Ph.D., Ignacio Varela, Ph.D., Benjamin Phillimore, B.Sc., Sharmin Begum, M.Sc., Neil Q. McDonald, Ph.D., Adam Butler, B.Sc., David Jones, M.Sc., Keiran Raine, M.Sc., Calli Latimer, B.Sc., Claudio R. Santos, Ph.D., Mahrokh Nohadani, H.N.C., Aron C. Eklund, Ph.D., Bradley Spencer-Dene, Ph.D., Graham Clark, B.Sc., Lisa Pickering, M.D., Ph.D., Gordon Stamp, M.D., Martin Gore, M.D., Ph.D., Zoltan Szallasi, M.D., Julian Downward, Ph.D., P. Andrew Futreal, Ph.D., and Charles Swanton, M.D., Ph.D.

A **Biopsy Sites**





B **Regional Distribution of Mutations**



CellPress

Review

Cancer Evolution and the Limits of Predictability in Precision Cancer Medicine

Kamil A. Lipinski,[1,3] Louise J. Barber,[1,3] Matthew N. Davies,[1] Matthew Ashenden,[1] Andrea Sottoriva,[1] and Marco Gerlinger[1,2,*]

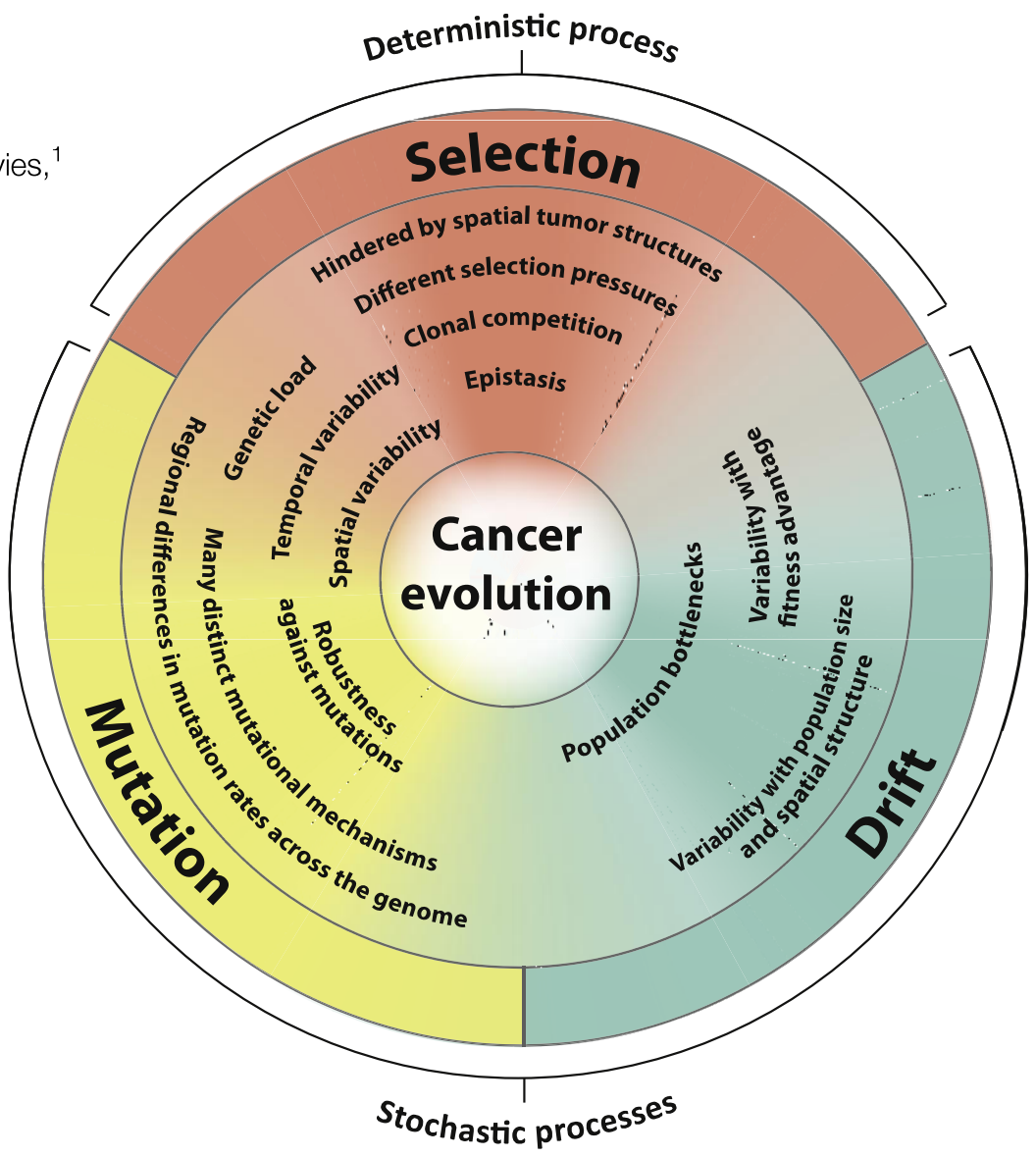


Table 4. Common EGFR TKI Resistance Mechanisms That Have Been Reported in Patient Samples

Mechanism	Gene	Alterations	Prevalence	Detection Method	References
EGFR-dominant	*EGFR*	SNV: T790M	41%-63%	LNA-PCR/sequencing assay	Hata et al., 2013[15]; Yu et al., 2013[16]
		SNV: D761Y, T854A, L747S	<5%	PCR-RFLP	Balak et al., 2006[78]; Bean et al., 2008[79]; Costa et al., 2007[80]
		Amplification	8%	FISH	Sequist et al., 2011
Bypass signalling tracts	*PIK3CA*	SNV	5%	SNaPshot	Sequist et al., 2011[14]
	BRAF	SNV	1%	SNaPshot	Ohashi et al., 2012[75]
	MET	Amplification	5%	FISH	Sequist et al., 2011[14]; Yu et al., 2013[16]
	HER2	Amplification	12%-13%	FISH	Takezawa et al., 2012[81]; Yu et al., 2013[16]
	AXL	Increased expression	20%	IHC	Zhang et al., 2012[82]
	HGF	Increased expression	61%	IHC	Yano et al., 2011[83]
	PTEN	Loss	10%	IHC	Yamamoto et al., 2010[84]
	—	Transition to EMT	16%-20%	IHC stain of vimentin and e-cadherin neuroendocrine markers	Sequist et al., 2011[14]; Zhang et al., 2012[82]

EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; *EGFR*, epidermal growth factor receptor gene; SNV, single nucleotide variation; LNA, locked nucleic acid; PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha gene; *BRAF*, B-Raf proto-oncogene, serine of threonine kinase gene; *MET*, MET proto-oncogene, receptor tyrosine kinase gene; FISH, fluorescence in situ hybridization; *HER2*, erb-b2 receptor tyrosine kinase 2 gene; *AXL*, AXL receptor tyrosine kinase gene; *HGF*, hepatocyte growth factor gene; IHC, immunohistochemistry; *RB1*, retinoblastoma 1 gene; EMT, epithelial-mesenchymal transition; PTEN, phosphatase and tensin homolog.

The cellular origins of drug resistance in cancer

Geoffrey R Oxnard

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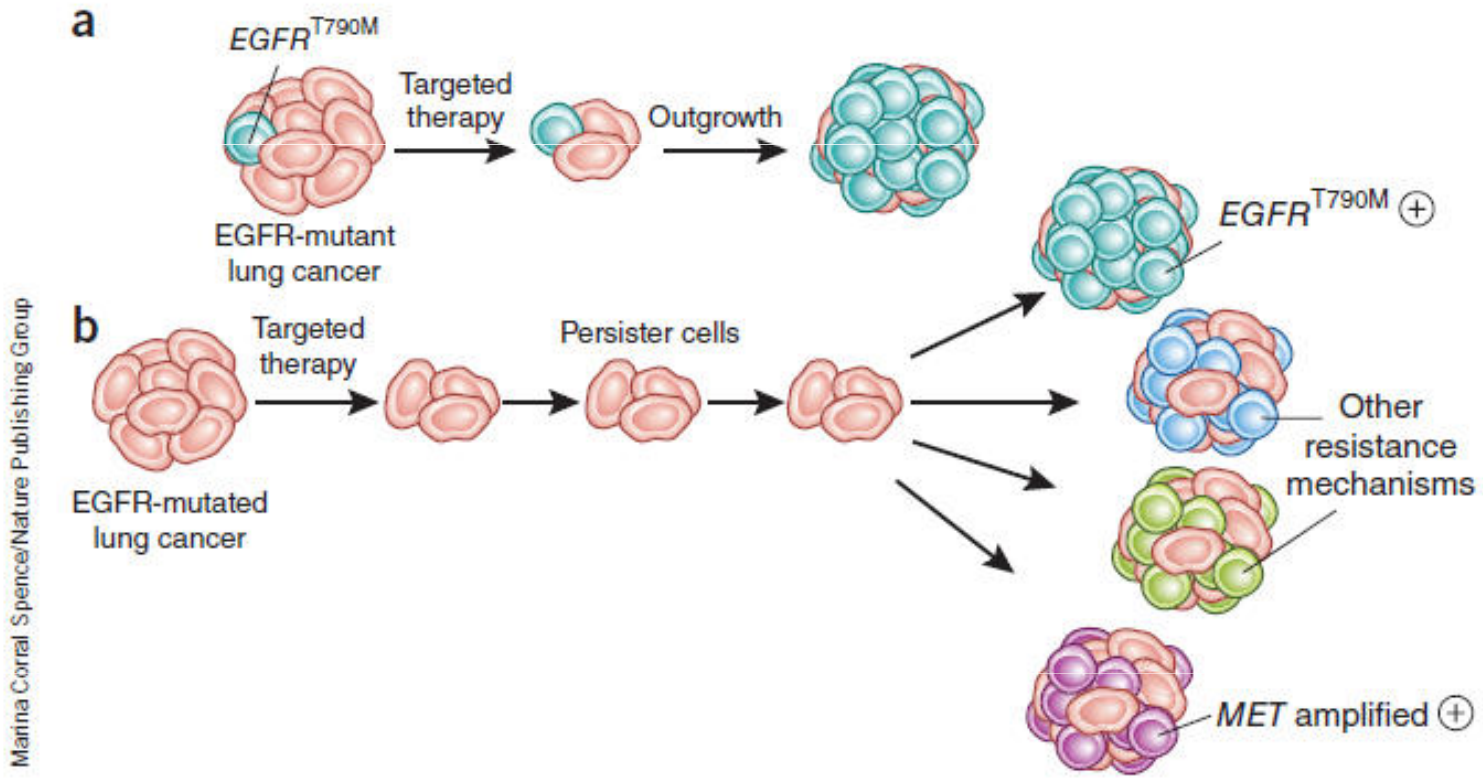


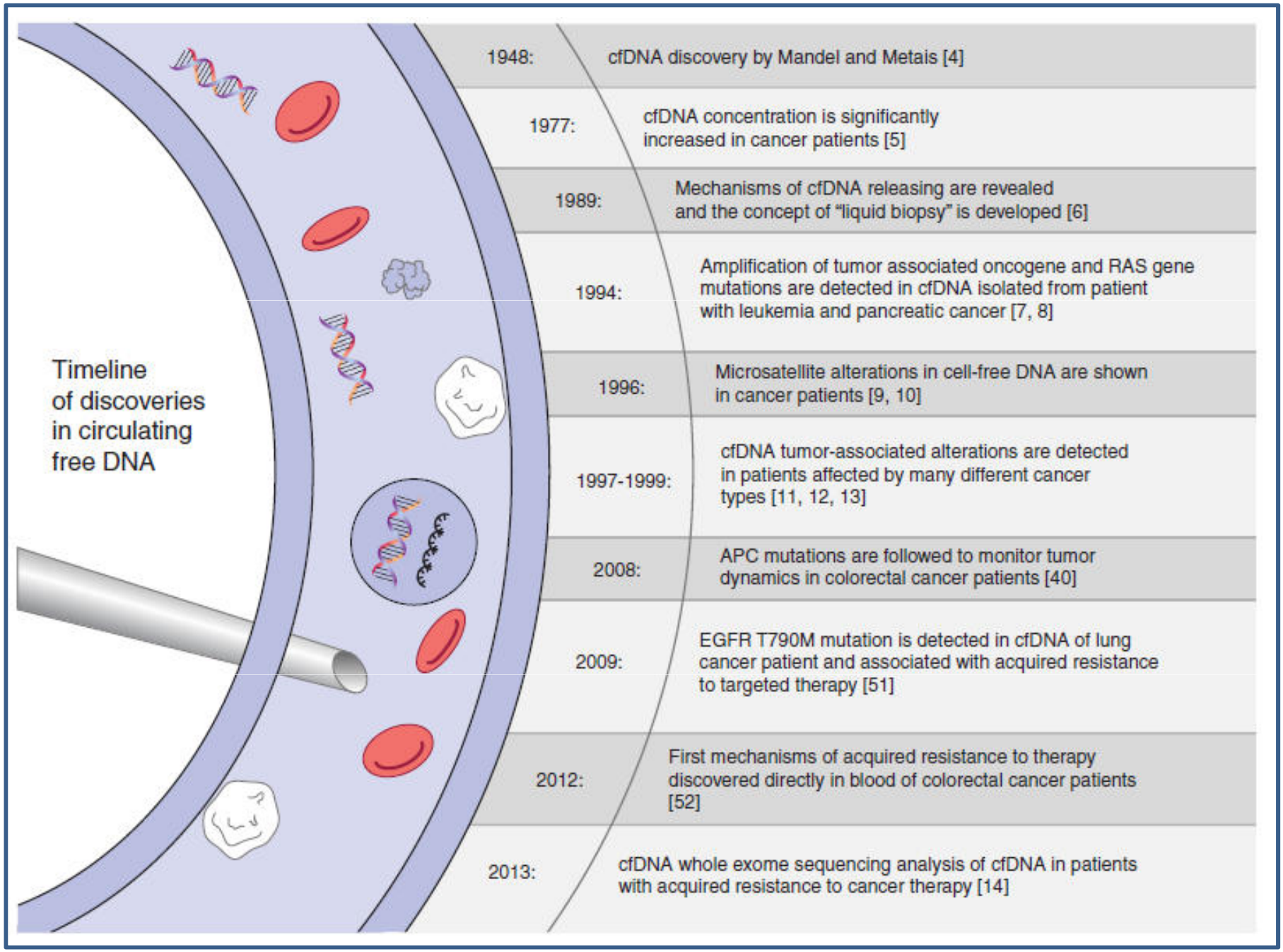
Figure 1 Differing biologies of acquired drug resistance. (**a**) Pre-existing subclones within a cancer can harbor a specific resistance mutation, such as *EGFR*^{T790M}. These resistant cells expand after an initial response to targeted therapy, resulting in the early development of a potentially predictable resistance mechanism. (**b**) In the absence of pre-existing resistant subclones, treatment with targeted therapy induces a more durable drug-tolerant state. With time, these 'persister' cells can acquire a variety of possible resistance mechanisms, such as *EGFR*^{T790M} or *MET* amplification, which makes the eventual resistance mechanism difficult to predict.

Biopsy: advantages

- Confirmation of diagnosis
- Evaluation of microinvorement
- IHC and FISH
- Molecular Testing Feasible

Biopsy: disadvantages

- Invasive
- Need to rescue tissue blocks
- Tumor Heterogenity
- Not suitable for therapeutic monitoring



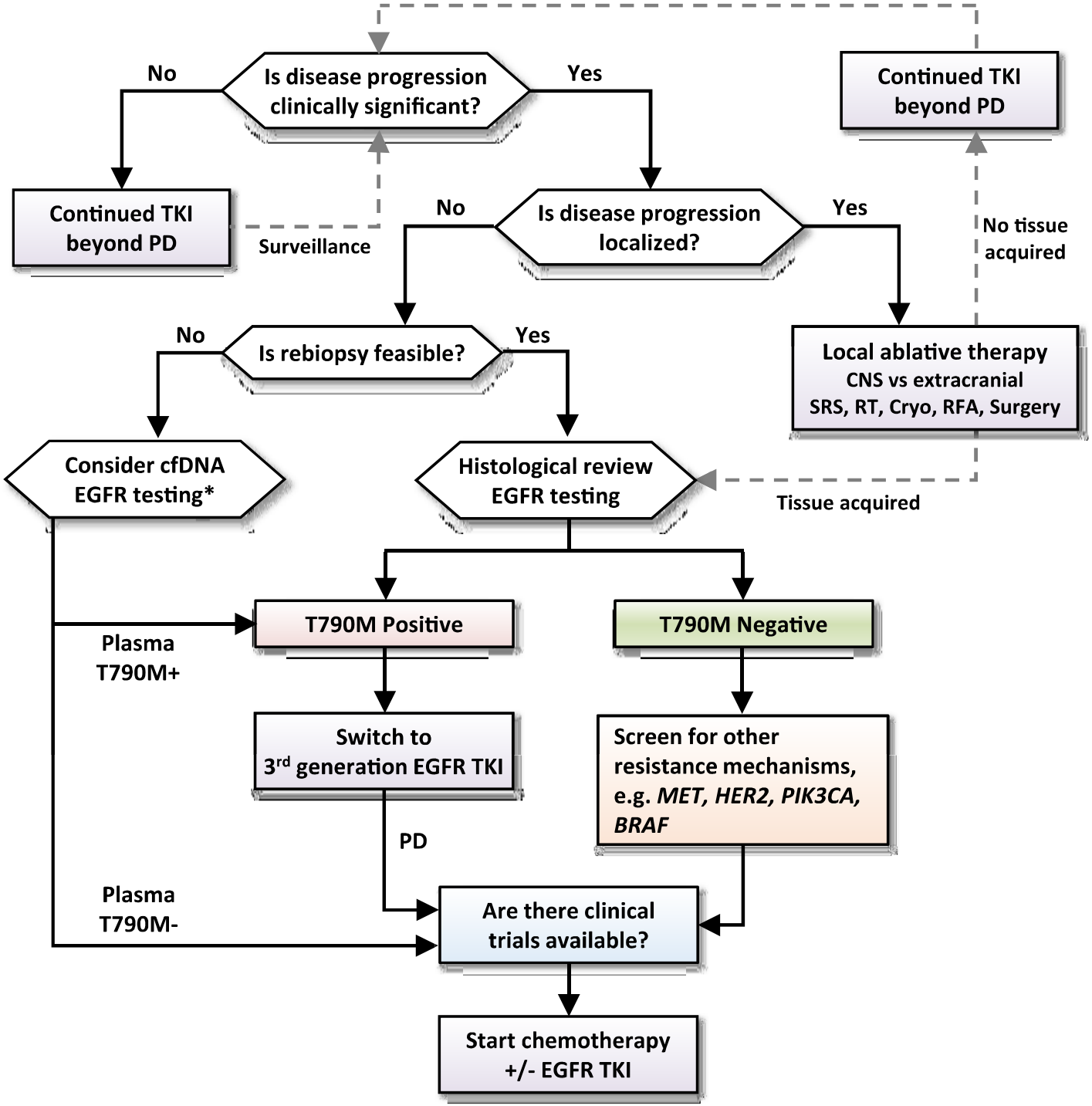
Siravegna and Bardelli Genome Biology 2014

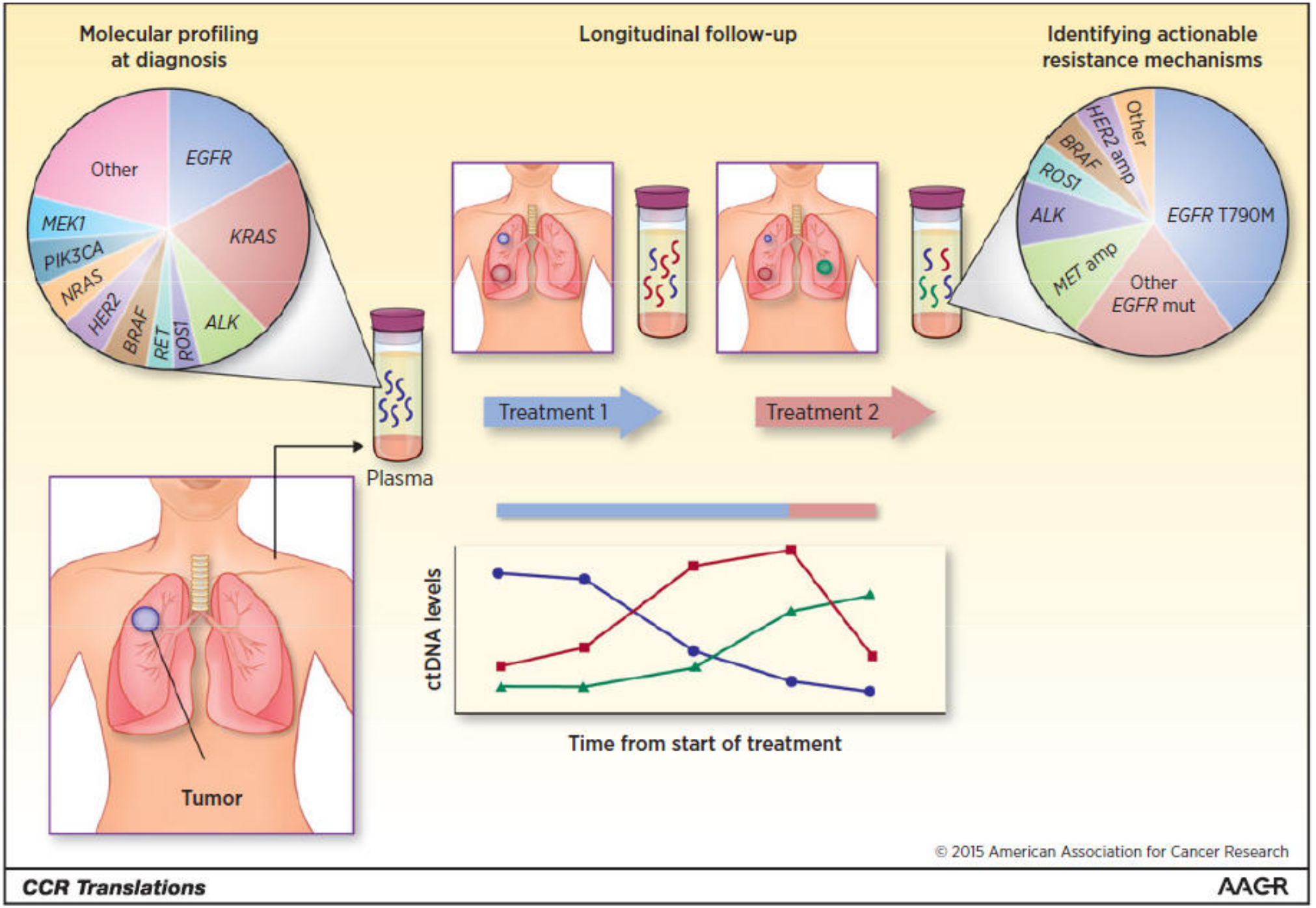
LB Advantages

- Non invasive
- ctDNA reflects genomic alterations of the tumor
- Recognizes tumor heterogenity
- Allows therapeutic monitoring
- Early identifiacation of resistant mutants

LB Disadvantages

- Does not separate tumor from normal circulating DNA
- False negatives (low sensitivity tools)
- False positives (high sensitivity tools)
- Non information on histology and microenviroment


Is disease progression clinically significant?
No
Yes
Continued TKI beyond PD
Continued TKI beyond PD
Surveillance
Is disease progression localized?
No
Yes
No tissue acquired
Local ablative therapy
CNS vs extracranial
SRS, RT, Cryo, RFA, Surgery
Is rebiopsy feasible?
No
Yes
Consider cfDNA EGFR testing*
Histological review EGFR testing
Tissue acquired
T790M Positive
T790M Negative
Plasma T790M+
Switch to 3rd generation EGFR TKI
Screen for other resistance mechanisms, e.g. MET, HER2, PIK3CA, BRAF
PD
Plasma T790M-
Are there clinical trials available?
Start chemotherapy +/- EGFR TKI



Tsui&Berger, Clin Cancer Res 2016

Table 1. Main mechanisms involved in acquired resistance to EGF receptor-tyrosine kinase inhibitors.

Molecular alteration	Frequency (%)†
T790M mutation	~50
MET amplification	5–20
EGFR amplification	8‡
HER2 amplification	5–13
MAPK1 amplification	4.8
PIK3CA mutations	5
BRAF mutations	1
AXL overexpression	20
GAS6 overexpression	25
EMT	1–2
SCLC transformation	5–14

†Frequencies are derived from different studies [5,9,22,37–41].
‡*EGFR* amplification + T790M mutation [37].
EMT: Epithelial-to-mesenchymal transition; SCLC: Small-cell lung carcinoma.

EGFR mutations in lung cancer: from tissue testing to liquid biopsy

Francesca Fenizia[1], Antonella De Luca[2], Raffaella Pasquale[1], Alessandra Sacco[1], Laura Forgione[1], Matilde Lambiase[1], Alessia Iannaccone[1], Nicoletta Chicchinelli[2], Renato Franco[3], Antonio Rossi[4], Alessandro Morabito[5], Gaetano Rocco[6], Maria Carmela Piccirillo[7] & Nicola Normanno*[1,2]

Future Oncol. (2015) 11(11), 1611–1623

Phenotipic Transformation

Only bioptic samples can prove it (5-14% dei casi)

Histologic biopsy still the Gold Standard for primary diagnosis and evaluation of metastatic disease

Histologic Transformation from Adenocarcinoma to Squamous Cell Carcinoma as a Mechanism of Resistance to EGFR Inhibition

Pavel A. Levin, MD, PhD, Melissa Mayer, RN,† Sharon Hoskin, APN,† Joseph Sailors, MD,‡*

Journal of Thoracic Oncology® • Volume 10, Number 9, September 2015

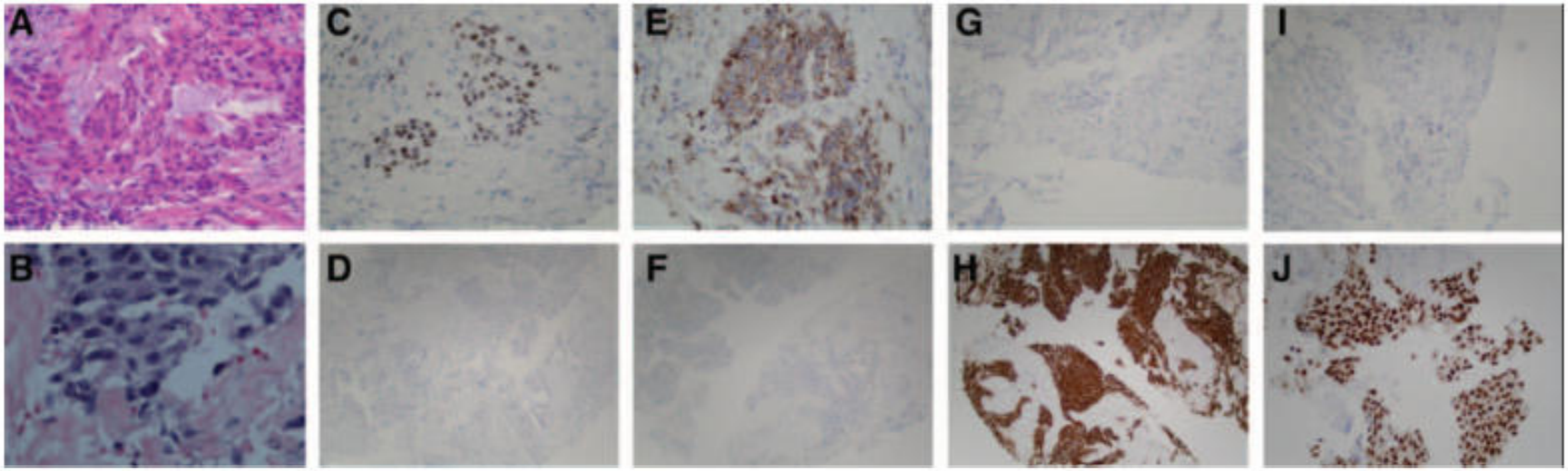


FIGURE 2. *A*, Pre-erlotinib treatment core needle biopsy of left lower lobe lesion demonstrating epithelial cells with pleomorphic nuclei and a mucoid background (hematoxylin and eosin, 400×). *B*, Post-erlotinib treatment core needle biopsy showing epithelioid cells with vacuolated cytoplasm, pleomorphic nuclei with occasional prominent nucleoli, and intercellular bridges (hematoxylin and eosin, 600×). *C*, Positive nuclear staining for thyroid transcription factor-1 in the pretreatment (400×) and (*D*) negative in the posttreatment biopsy (200×). *E*, Positive cytoplasmic staining for Napsin A in the pretreatment (400×) and (*F*) negative in the posttreatment biopsy (200X). *G*, Negative staining for CK5/6 in the pretreatment (200×) and (*H*) positive stain in the posttreatment biopsy (200×). *I*, Negative staining for p63 in the pretreatment (200×) and (*J*) positive nuclear staining in the posttreatment core needle biopsy (200×).

Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial

Roy S Herbst, Paul Baas, Dong-Wan Kim, Enriqueta Felip, José L Pérez-Gracia, Ji-Youn Han, Julian Molina, Joo-Hang Kim, Catherine Dubos Arvis, Myung-Ju Ahn, Margarita Majem, Mary J Fidler, Gilberto de Castro Jr, Marcelo Garrido, Gregory M Lubiniecki, Yue Shentu, Ellie Im, Marisa Dolled-Filhart, Edward B Garon

Lancet 2016; 387: 1540–50

Published Online December 19, 2015

Summary

Background Despite recent advances in the treatment of advanced non-small-cell lung cancer, there remains a need for effective treatments for progressive disease. We assessed the efficacy of pembrolizumab for patients with previously treated, PD-L1-positive, advanced non-small-cell lung cancer.

Interpretation Pembrolizumab prolongs overall survival and has a favourable benefit-to-risk profile in patients with previously treated, PD-L1-positive, advanced non-small-cell lung cancer. These data establish pembrolizumab as a new treatment option for this population and validate the use of PD-L1 selection.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

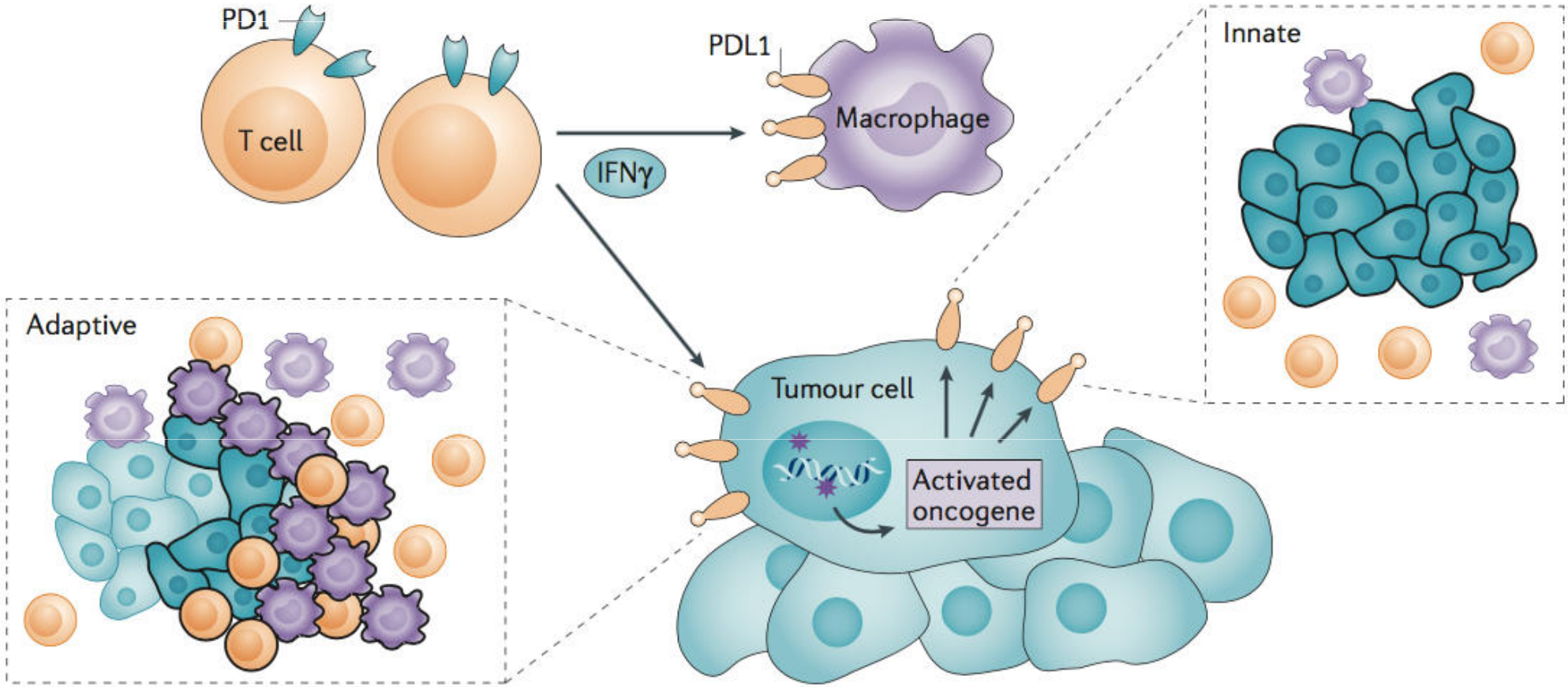
Pembrolizumab versus Chemotherapy for PD-L1–Positive Non–Small-Cell Lung Cancer

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*

CONCLUSIONS

In patients with advanced NSCLC and PD-L1 expression on at least 50% of tumor cells, pembrolizumab was associated with significantly longer progression-free and overall survival and with fewer adverse events than was platinum-based chemotherapy. (Funded by Merck; KEYNOTE-024 ClinicalTrials.gov number, NCT02142738.)

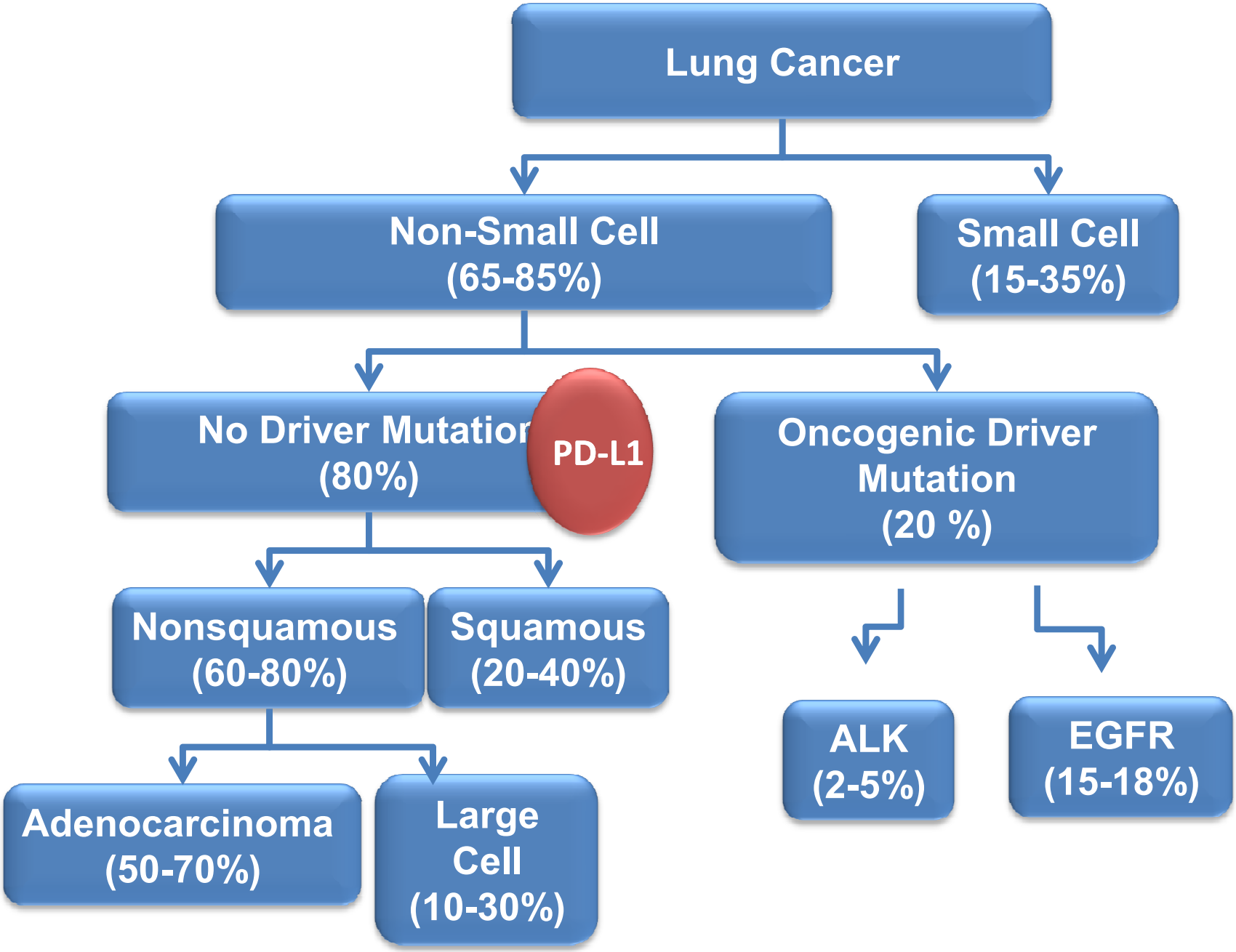
PDL1
Intratumoral Expression



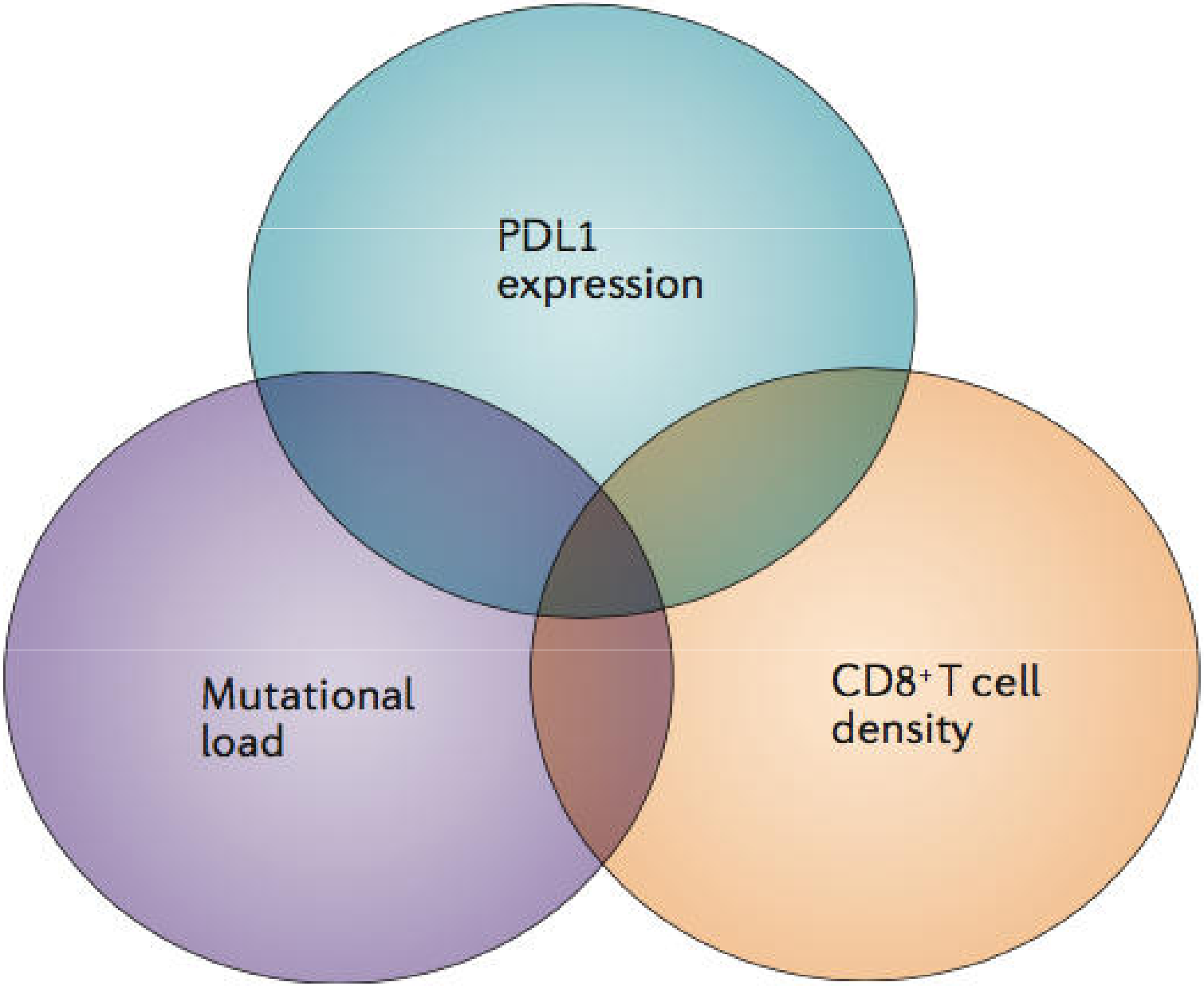
PDL1 Testing

- Required for selection of patients with NSCLC to be treated with Pembrolizumab
  - First line: > 50% positive cells
  - Second line: > 1% positive cells
- Not required for Nivolumab in NSCLC (second line)
- Not required in Melanoma

Lung Cancer

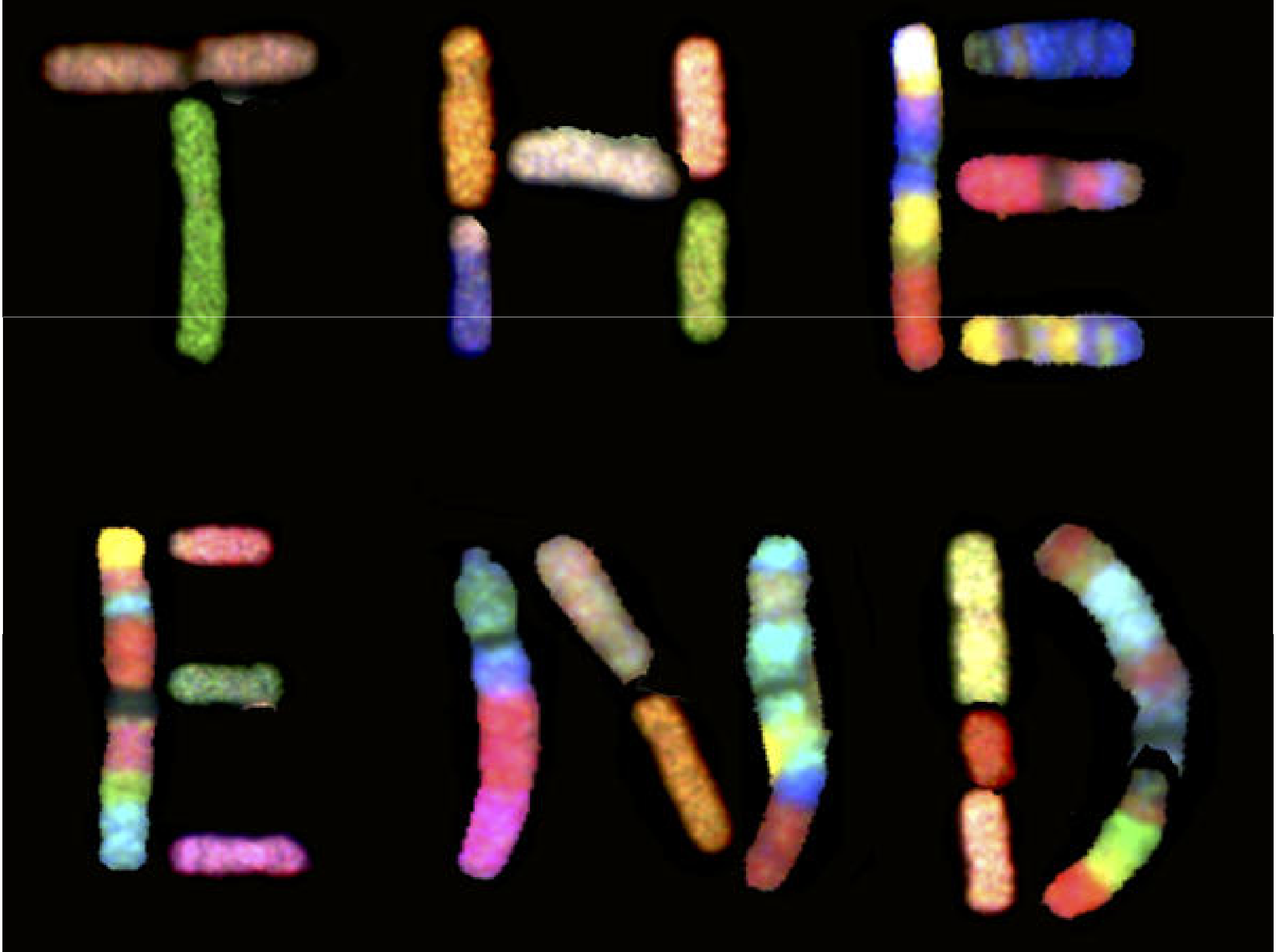

Lung Cancer
Non-Small Cell (65-85%)
Small Cell (15-35%)
No Driver Mutation (80%)
PD-L1
Oncogenic Driver Mutation (20 %)
Nonsquamous (60-80%)
Squamous (20-40%)
Adenocarcinoma (50-70%)
Large Cell (10-30%)
ALK (2-5%)
EGFR (15-18%)

PD1/PD-L1 is a reliable biomarker alone?



Take home messages

- Accurate morphologic diagnosis
- Wise use of bioptic samples
- Immunomorphologic definition of histotype
- Identification of driver mutations (EGFR, KRAS, ALK, ROS1)
- PDL1
- Liquid Biopsy of identification of T790M
- Careful re-organization of diagnostic flo-chart


THE
END