New molecular targets in lung cancer therapy

Giuseppe Pelosi

University of Milan

Pathology Division, Science & Technology Park, IRCCS Multimedica, Milan

Advanced lung cancer (IIIB – IV)

- **Subtyping**
- **Oncogene addiction** (EGFR, ALK, ROS1)
- **Clinics** (age, PS, comorbidities)

No oncogene addiction

- **Subtyping**
- **PD-L1 expression (TPS)**
- **Clinics** (age, PS, comorbidities)

Linee guida

NEOPLASIE DEL POLMONE

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Aiom

Associazione Italiana di Oncologia Medica

Advanced lung cancer: subtyping

ΔNp63 (p40) Distribution Inside Lung Cancer: A Driver Biomarker Approach to Tumor Characterization

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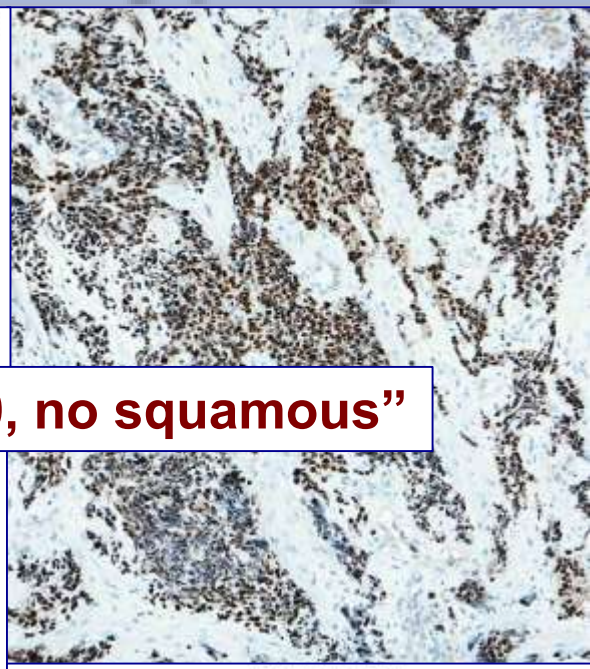
Giuseppe Pelosi, MD, MIAC[1,2], Giulio Rossi, MD[3], Alberto Cavazza, MD[3], Luisella Righi, MD[4], Patrick Maisonneuve, Eng[5], Mattia Barbareschi, MD[6], Paolo Graziano, MD[7], Ugo Pastorino, MD[1], Marina Garassino, MD[1], Filippo de Braud, MD[1], and Mauro Papotti, MD[4]



"no p40, no squamous"

A

p40 Histologic Score (n=146)

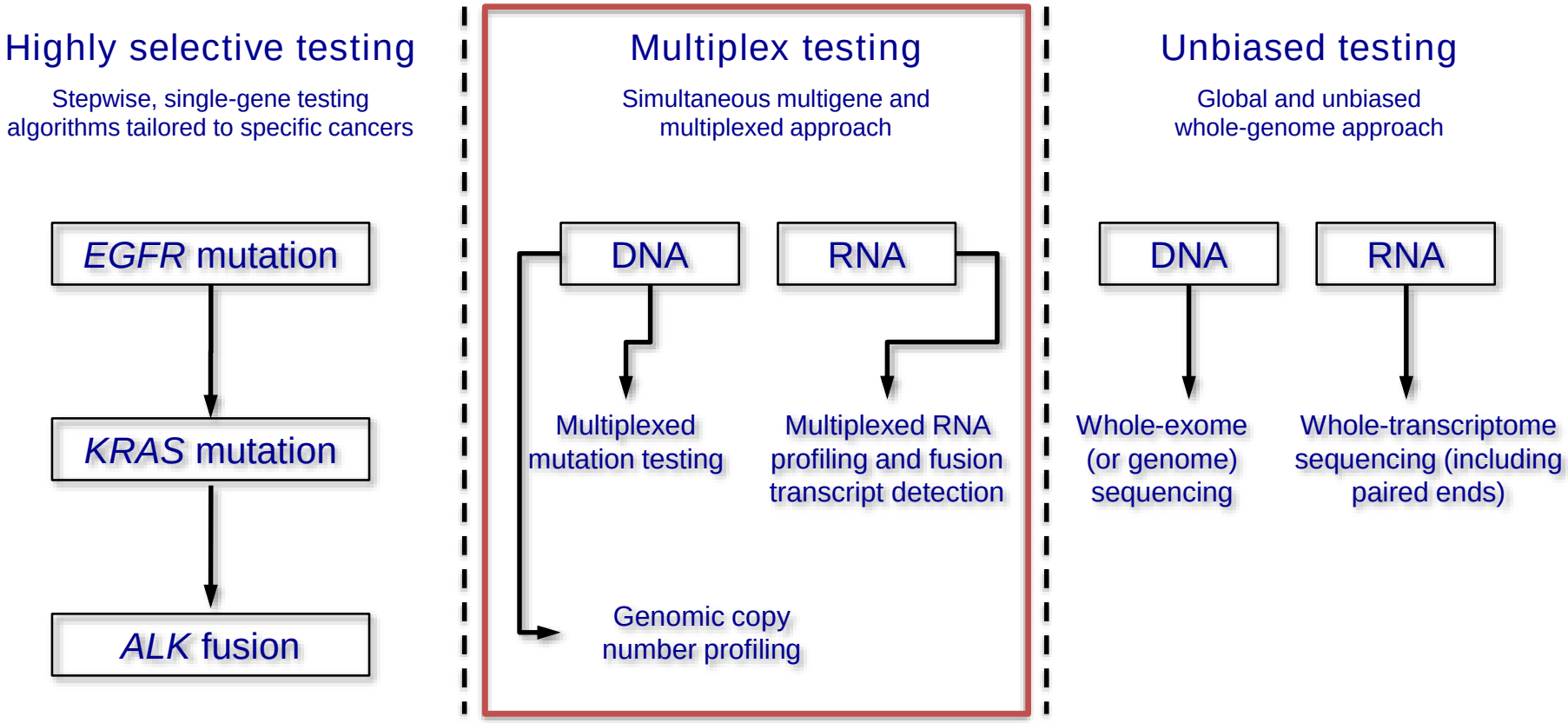
- HS ≤10 negative category (n=106)
  - AD (n=71)
  - PLC-AD (n=11) CS-AD (n=2)
  - SCLC (n=10) LCNEC (n=5) Carcinoid (n=2)
  - MEM (n=5)
- HS = 11-50 1+ category (n=1)
  - AD (n=1)
- HS = 51-100 2+ category (n=3)
  - ADSQC (n=3)#
- HS >100 3+ category (n=36)
  - SQC (n=27)
  - B-LCC (n=3)
  - PLC-SQC (n=2)**
  - ADSQC (n=2)*
  - SGTT (n=2)
  - ADCC (n=1)
  - MEC (n=

NON-SQUAMOUS

SQUAMOUS

	p40 Immunoreactivity				
	HS ≤ 10	HS = 11-50	HS = 51-100	HS > 100	
Variable	Negative	1+	2+	3+	P
			= 3	n = 36	<.00001
			0	0	
			0	27	
			0	2	
CS	2	0	0	0	
SCLC	10	0	0	0	
LCNEC	5	0	0	0	
Carcinoid	2	0	0	0	
B-LCC	0	0	0	3	
ADSQC	0	0	3	2	
SGTT	0	0	0	2	
MEM	5	0	0	0	
Cell differentiation	n = 126	n = 2	n = 0	n = 40	<.00001
lineage					
Squamous	0	0	0	38	
Glandular	90	1	0	0	
Neuroendocrine	18	0	0	0	
Myoepithelial	0	0	0	1	
EMT	13	1	0	1	
Mesothelial	5	0	0	0	

Molecular diagnostics



Present → Future

Taylor BS & Ladanyi M – J Pathol 2011

Multiplex testing by targeted NGS

Oncomine Comprehensive Assay v3

Hotspot genes

AKT1, ALK, AR, ARAF, BRAF, BTK, CBL, CDK4, CHEK2, CSF1R, CTNNB1, DDR2, EGFR, ERBB2, ERB83, ERBB4, ESR1, EZH2, FGFR1, FGFR2, FGFR3, FLT3, FOXL2, GATA2, GNA11, GNAQ, GNAS, HNF1A, HRAS, IDH1, IDH2, JAK1, JAK2, JAK3, KDR, KIT, KNSTRN, KRAS, MAGOH, MAP2K1, MAP2K2, MAPK1, MAX, MED12, MET, MTOR, MYD88, NFE2L2, NRAS, PDGFRA, PIK3CA, PPP2R1A, PTPN11, RAC1, RAF1, RET, RHEB, RHOA, SF3B1, SMO, SPOP, SRC, STAT3, U2AF1, XPO1, AKT2, AKT3, AXL, CCND1, CDK6, ERCC2, FGFR4, H3F3A, HIST1H3B, MAP2K4, MDM4, MYC, MYCN, NTRK1, NTRK2, PDGFRB, PIK3CB, ROS1, SMAD4, TERT, TOP1

Full-length genes

ATM, BAP1, BRCA1, BRCA2, CDKN2A, FBXW7, MSH2, NF1, NF2, NOTCH1, PIK3R1, PTCH1, PTEN, RB1, SMARCB1, STK11, TP53, TSC1, TSC2, ARID1A, ATR, ATRX, CDK12, CDKN1B, CDKN2B, CHEK1, CREBBP, FANCA, FANCD2, FANCI, MLH1, MRE11A, MSH6, NBN, NOTCH2, NOTCH3, PALB2, PMS2, POLE, RAD50, RAD51, RAD51B, RAD51C, RAD51D, RNF43, SETD2, SLX4, SMARCA4

161 unique cancer driver genes

Copy number genes

AKT1, AR, CCND1, CCNE1, CDK4, CDK6, EGFR, ERBB2, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, IGF1R, KIT, KRAS, MDM2, MDM4, MET, MYC, MYCL, MYCN, PDGFRA, PIK3CA, PPARG, TERT, AKT2, AKT3, ALK, AXL, BRAF, CCND2, CCND3, CDK2, CDKN2A, CDKN2B, ESR1, FGF19, FGF3, NTRK1, NTRK2, NTRK3, PDGFRB, PIK3CB, RICTOR, TSC1, TSC2

Gene fusions (inter- and intragenic)

ALK, AXL, BRAF, EGFR, ERBB2, ERG, ETV1, ETV4, ETV5, FGFR1, FGFR2, FGFR3, NTRK1, NTRK3, PDGFRA, PPARG, RAF1, RET, ROS1, AKT2, AR, BRCA1, BRCA2, CDKN2A, ERB84, ESR1, FGR, FLT3, JAK2, KRAS, MDM4, MET, MYB, MYBL1, NF1, NOTCH1, NOTCH4, NRG1, NTRK2, NUTM1, PDGFRB, PIK3CA, PRKACA, PRKACB, PTEN, RAD51B, RB1, RELA, RSPO2, RSPO3, TERT

Oncomine Focus Assay

CATEGORIZED BY SOMATIC ALTERATION TYPE

52 GENES

CATEGORIZED BY PUBLISHED RELEVANCE

Hotspot mutations

AKT1, ALK, AR, BRAF, CDK4, CTNNB1, DDR2, EGFR, ERBB2, ERBB3, ERBB4, ESR1, FGFR2, FGFR3, GNA11, GNAQ, HRAS, IDH1, IDH2, JAK1, JAK2, JAK3, KIT, KRAS, MAP2K1, MAP2K2, MET, MTOR, NRAS, PDGFRA, PIK3CA, RAF1, RET, ROS1, SMO

Focal CNV gains

ALK, AR, BRAF, CCND1, CDK4, CDK6, EGFR, ERBB2, FGFR1, FGFR2, FGFR3, FGFR4, KIT, KRAS, MET, MYC, MYCN, PDGFRA, PIK3CA

Fusion drivers

ABL1, AKT3, ALK, AXL, BRAF, EGFR, ERBB2, ERG, ETV1, ETV4, ETV5, FGFR1, FGFR2, FGFR3, MET, NTRK1, NTRK2, NTRK3, PDGFRA, PPARG, RAF1, RET, ROS1

Labels

ALK, BRAF, EGFR, ERBB2, KRAS, NRAS

Guidelines

ALK, BRAF, EGFR, ERBB2, KIT, KRAS, MET, NRAS, PDGFRA, RET, ROS1

Drug targets

ABL1, AKT1, AKT3, ALK, AR, AXL, BRAF, CCND1, CDK4, CDK6, CTNNB1, DDR2, EGFR, ERBB2, ERBB3, ERBB4, ESR1, FGFR1, FGFR2, FGFR3, FGFR4, IDH1, IDH2, JAK1, JAK2, JAK3, KIT, KRAS, MAP2K1, MAP2K2, MET, MTOR, MYC, NTRK1, NTRK2, NTRK3, PDGFRA, PIK3CA, PPARG, RAF1, RET, ROS1, SMO

Advanced lung cancer (IIIB – IV)

Updated Molecular Testing Guideline for the Selection of Lung Cancer Patients for Treatment With Targeted Tyrosine Kinase Inhibitors

Guideline From the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology

Journal of Thoracic Oncology 2017

Neal I. Lindeman, MD,[a,*] Philip T. Cagle, MD,[c] Dara L. Aisner, MD, PhD,[d] Maria E. Arcila, MD,[e] Mary Beth Beasley, MD,[g] Eric Bernicker, MD,[h] Carol Colasacco, MLIS, SCT(ASCP),[i] Sanja Dacic, MD, PhD,[j] Fred R. Hirsch, MD, PhD,[k] Keith Kerr, MB, ChB,[l] David J. Kwiatkowski, MD, PhD,[b] Marc Ladanyi, MD,[f] Jan A. Nowak, MD, PhD,[m] Lynette Sholl, MD,[a] Robyn Temple-Smolkin, PhD,[n] Benjamin Solomon, MBBS, PhD,[o] Lesley H. Souter, PhD,[p] Erik Thunnissen, MD, PhD,[q] Ming S. Tsao, MD,[r] Christina B. Ventura, MPH, MT(ASCP),[i] Murry W. Wynes, PhD,[s] Yasushi Yatabe, MD, PhD[t]

- "***Testing should extend beyond those molecular alterations for which targeted therapies are approved by regulatory agencies***…**to include molecular alterations for which there is compelling evidence of effective investigational targeted therapies (and, more recently, immunotherapies) from published clinical trials**"

Lindeman et al, JTO 2017

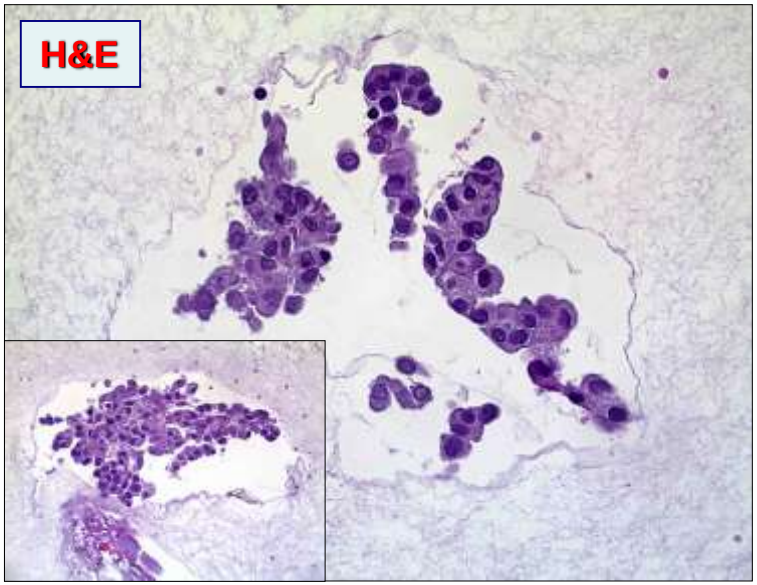
Advanced lung cancer (IIIB – IV)

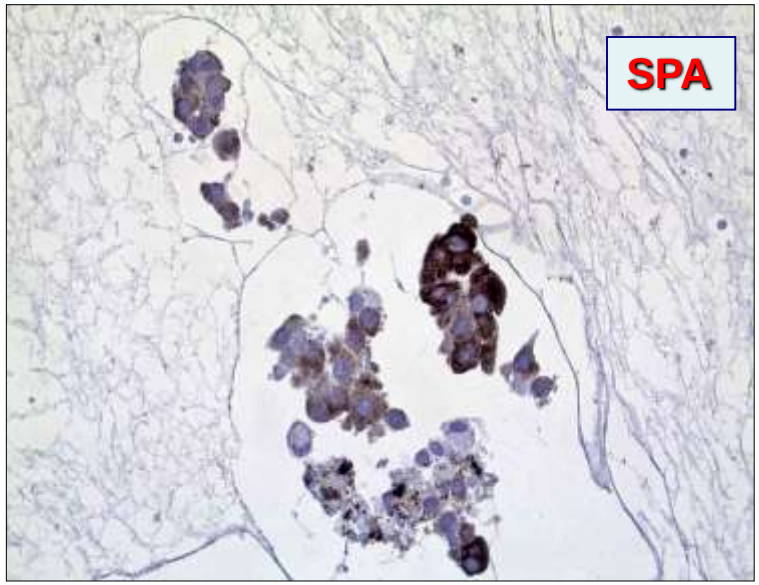
- "Must-test" biomarkers: EGFR, ALK, ROS1, PD-L1 by all laboratories
- "Should-test" biomarkers: an expanded panel (BRAF, MET, RET, HER2, KRAS)
- "Investigational" biomarkers: all the other genes

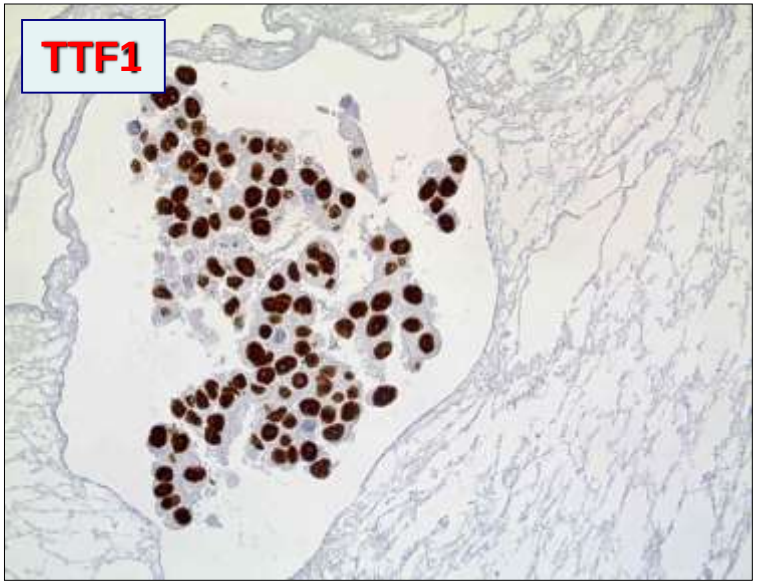
Table 3. Summary of the Updated Statements With Strength of Recommendations[a]

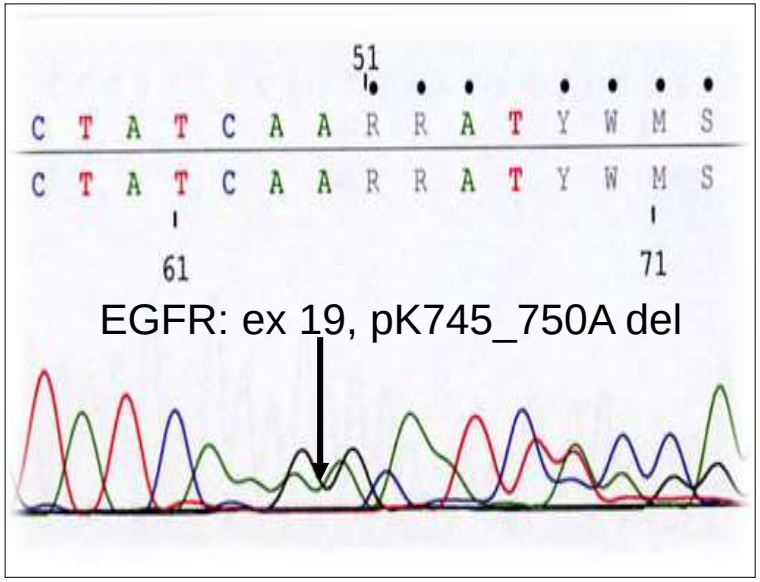
2013 Statement	2017 Statement
Expert consensus opinion: Cytologic samples are also suitable for EGFR and ALK testing, with cell blocks being preferred over smear preparations.	Recommendation: Pathologists may use either cell blocks or other cytologic preparations as suitable specimens for lung cancer biomarker molecular testing.
Expert consensus opinion: Laboratories should use EGFR test methods that are able to detect mutations in specimens with at least 50% cancer cell content, although laboratories are strongly encouraged to use (or have available at an external reference laboratory) more sensitive tests that are able to detect mutations in specimens with as little as 10% cancer cells.	Expert consensus opinion: Laboratories should use, or have available at an external reference laboratory, clinical lung cancer biomarker molecular testing assays that are able to detect molecular alterations in specimens with as little as 20% cancer cells.
Recommendation: Immunohistochemistry for total EGFR is not recommended for selection of EGFR TKI therapy.	Strong recommendation: Laboratories should not use total EGFR expression by IHC testing to select patients for EGFR-targeted TKI therapy.

Advanced lung cancer (IIIB – IV)



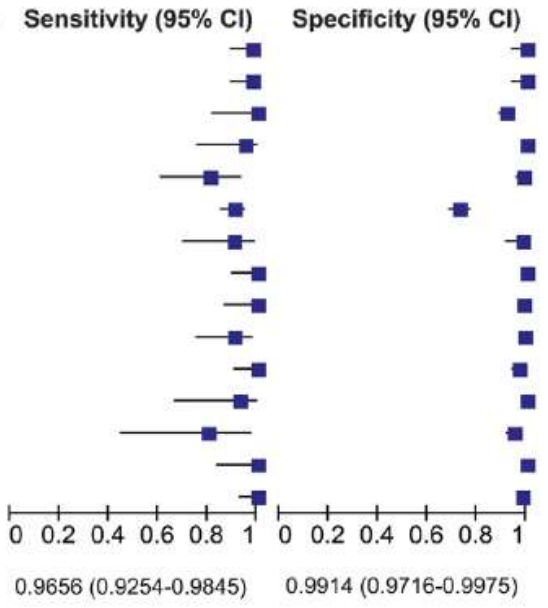




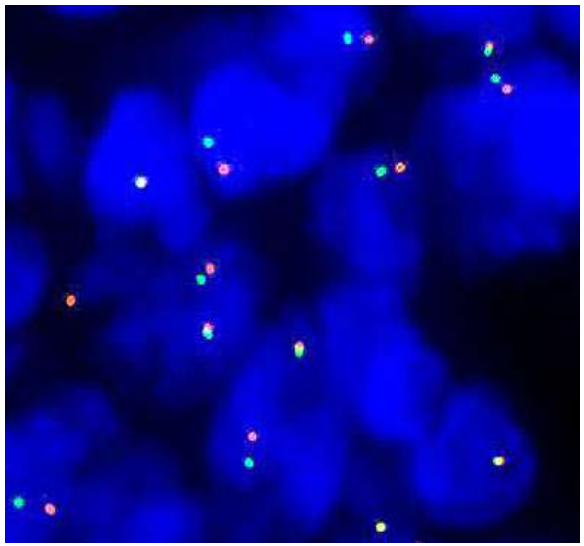


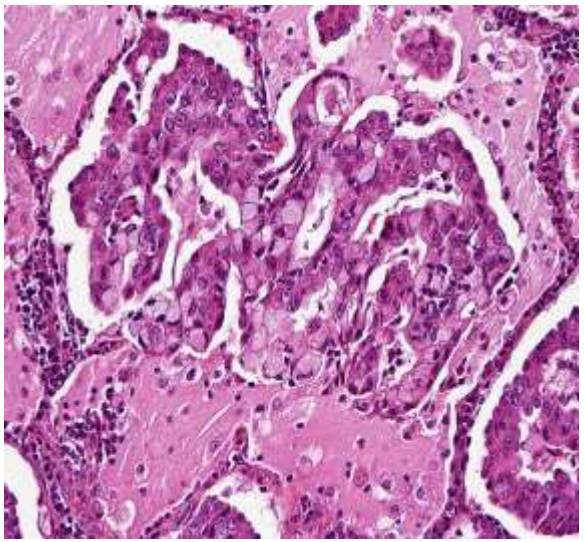
Advanced lung cancer: ALK

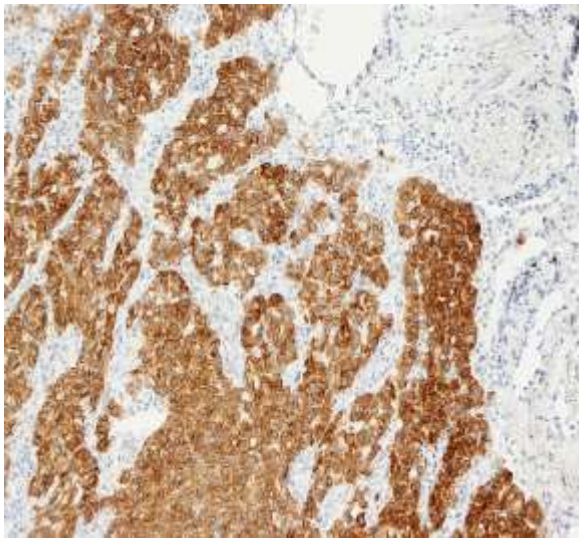
Study	TP	FP	FN	TN	Antibody	Cut-Off	Sensitivity (95% CI)	Specificity (95% CI)
Conde 2014[145]	46	0	1	56	5A4	2-3+	0.98 [0.89, 1.00]	1.00 [0.94, 1.00]
Conde 2014b[145]	46	0	1	56	D5F3	2-3+	0.98 [0.89, 1.00]	1.00 [0.94, 1.00]
Cutz 2014[146]	18	29	0	326	5A4	At least 1+	1.00 [0.81, 1.00]	0.92 [0.88, 0.94]
Gruber 2015[153]	19	0	1	198	D5F3	At least 1+	0.95 [0.75, 1.00]	1.00 [0.98, 1.00]
Ilie 2015[61]	21	2	5	149	5A4	At least 1+	0.81 [0.61, 0.93]	0.99 [0.95, 1.00]
Lantuejoul 2015[154]	127	108	13	292	5A4/D5F3	At least 1+	0.91 [0.85, 0.95]	0.73 [0.68, 0.77]
McLeer-Florin 2012[139]	19	1	2	59	5A4	At least 1+	0.90 [0.70, 0.99]	0.98 [0.91, 1.00]
Minca 2013[142]	32	0	0	217	D5F3	pos or neg	1.00 [0.89, 1.00]	1.00 [0.98, 1.00]
Park 2012[141]	25	3	0	234	5A4	At least 1+	1.00 [0.86, 1.00]	0.99 [0.96, 1.00]
Savic 2015[155]	29	2	3	269	5A4/D5F3	At least 1+	0.91 [0.75, 0.98]	0.99 [0.97, 1.00]
Shan 2014[151]	36	8	0	242	D5F3	pos or neg	1.00 [0.90, 1.00]	0.97 [0.94, 0.99]
Sholl 2013[140]	13	0	1	162	5A4	pos or neg	0.93 [0.66, 1.00]	1.00 [0.98, 1.00]
Tantraworasin 2014[147]	8	13	2	244	5A4	pos or neg	0.80 [0.44, 0.97]	0.95 [0.92, 0.97]
To 2013[143]	20	0	0	331	5A4	2-3+	1.00 [0.83, 1.00]	1.00 [0.99, 1.00]
Wang 2014[148]	46	7	0	377	D5F3	At least 1+	1.00 [0.92, 1.00]	0.98 [0.96, 0.99]



IHC 2+/3+ using mAb 5A4 and/or D5F3

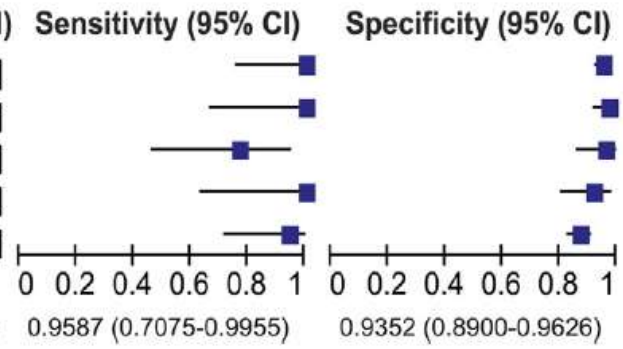




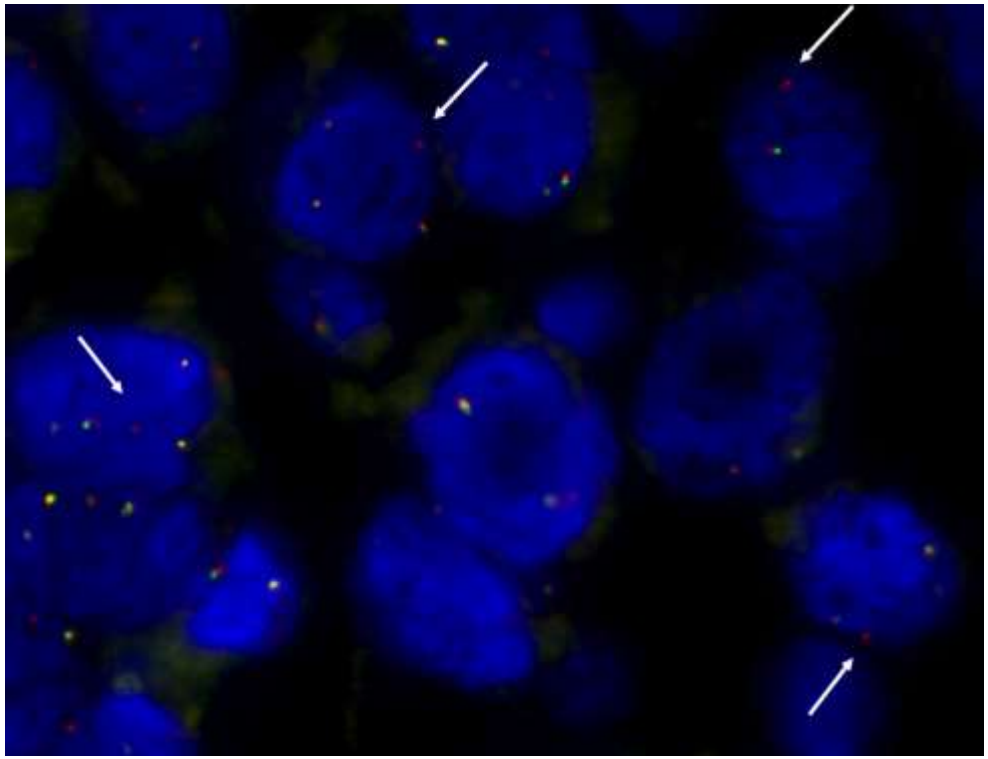


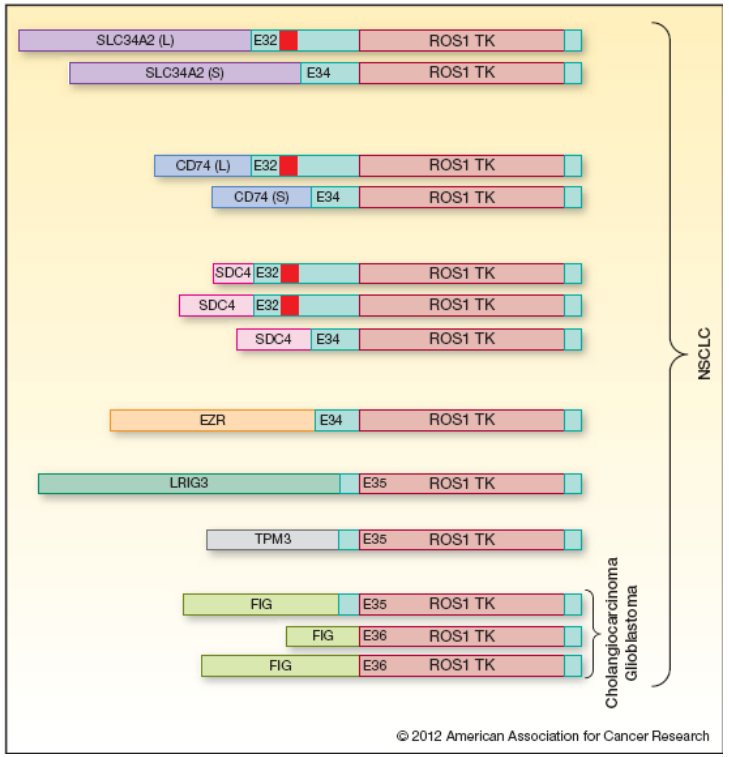
Advanced lung cancer: ROS-1

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Cha 2014[42]	13	16	0	301	1.00 [0.75, 1.00]	0.95 [0.92, 0.97]
Mescam-Mancini 2014[43]	9	3	0	95	1.00 [0.66, 1.00]	0.97 [0.91, 0.99]
Shan 2015[47]	10	2	3	45	0.77 [0.46, 0.95]	0.96 [0.85, 0.99]
Sholl 2013[44]	8	4	0	44	1.00 [0.63, 1.00]	0.92 [0.80, 0.98]
Yoshida 2014[45]	16	33	1	220	0.94 [0.71, 1.00]	0.87 [0.82, 0.91]



IHC 2+/3+ using mAb D4D6





"Should-test" biomarkers

Table 4. Summary of 2017 Guideline Statements — **Lindeman et al, JTO 2017**

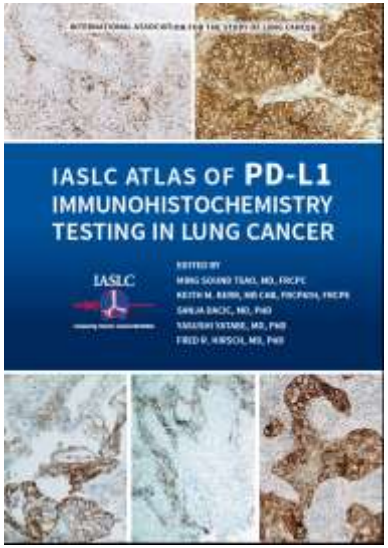
Guideline Statements	Strength of Recommendation
Key Question 1: Which new genes should be tested for lung cancer patients?	
1. *ROS1* testing must be performed on all lung adenocarcinoma patients, irrespective of clinical characteristics.	Strong recommendation
2. ROS1 IHC may be used as a screening test in lung adenocarcinoma patients; however, positive ROS1 IHC results should be confirmed by a molecular or cytogenetic method.	Expert consensus opinion
3. *BRAF* molecular testing is currently not indicated as a routine stand-alone assay outside the context of a clinical trial. It is appropriate to include *BRAF* as part of larger testing panels performed either initially or when routine *EGFR*, *ALK*, and *ROS1* testing are negative.	Expert consensus opinion
4. *RET* molecular testing is not recommended as a routine stand-alone assay outside the context of a clinical trial. It is appropriate to include *RET* as part of larger testing panels performed either initially or when routine *EGFR*, *ALK*, and *ROS1* testing are negative.	Expert consensus opinion
5. *ERBB2* (*HER2*) molecular testing is not indicated as a routine stand-alone assay outside the context of a clinical trial. It is appropriate to include *ERBB2* (*HER2*) mutation analysis as part of a larger testing panel performed either initially or when routine *EGFR*, *ALK*, and *ROS1* testing are negative.	Expert consensus opinion
6. *KRAS* molecular testing is not indicated as a routine stand-alone assay as a sole determinant of targeted therapy. It is appropriate to include *KRAS* as part of larger testing panels performed either initially or when routine *EGFR*, *ALK*, and *ROS1* testing are negative.	Expert consensus opinion
7. *MET* molecular testing is not indicated as a routine stand-alone assay outside the context of a clinical trial. It is appropriate to include *MET* as part of larger testing panels performed either initially or when routine *EGFR*, *ALK*, and *ROS1* testing are negative.	Expert consensus opinion

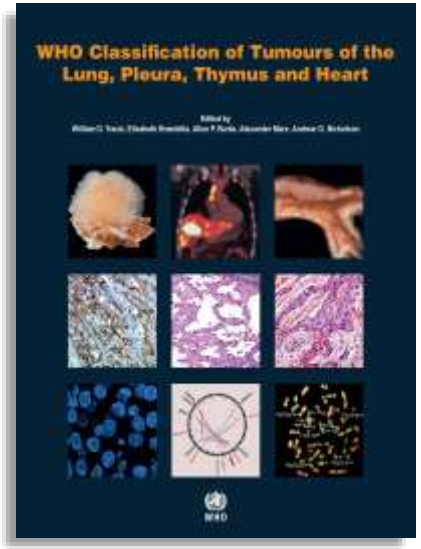
"Investigational" biomarkers

Table 5. Emerging Markers for Molecular Testing in Lung Cancer — Lindeman et al, JTO 2017
Mitogen-activated protein kinase kinase 1 (*MEK1/MAP2K1*)
Fibroblast growth factor receptor 1-4 (*FGFR 1-4*)
Neurotrophic tyrosine kinase, receptor, type 1-3 (*NTRK1-3*)
Neuregulin 1 (*NRG1*)
Ras-like without CAAX 1 (*RIT1*)
Neurofibromin 1 (*NF1*)
Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (*PIK3CA*)
AKT serine/threonine kinase 1 (*AKT1*)
NRAS proto-oncogene, GTPase (*NRAS*)
Mechanistic target of rapamycin (*MTOR*)
Tuberous sclerosis 1 (*TSC1*)
Tuberous sclerosis 2 (*TSC2*)
KIT proto-oncogene receptor tyrosine kinase (*KIT*)
Platelet-derived growth factor receptor alpha (*PDGFRA*)
Discoidin domain receptor tyrosine kinase 2 (*DDR2*)

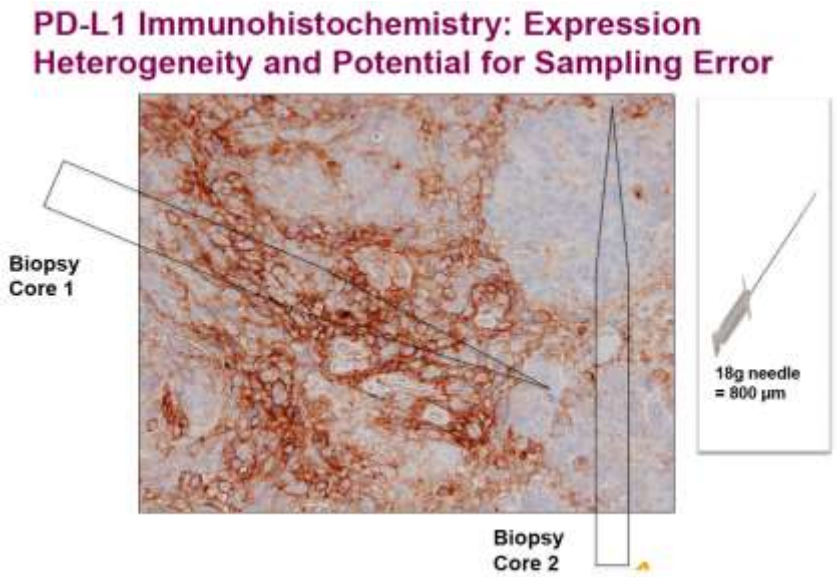
Molecular biomarkers

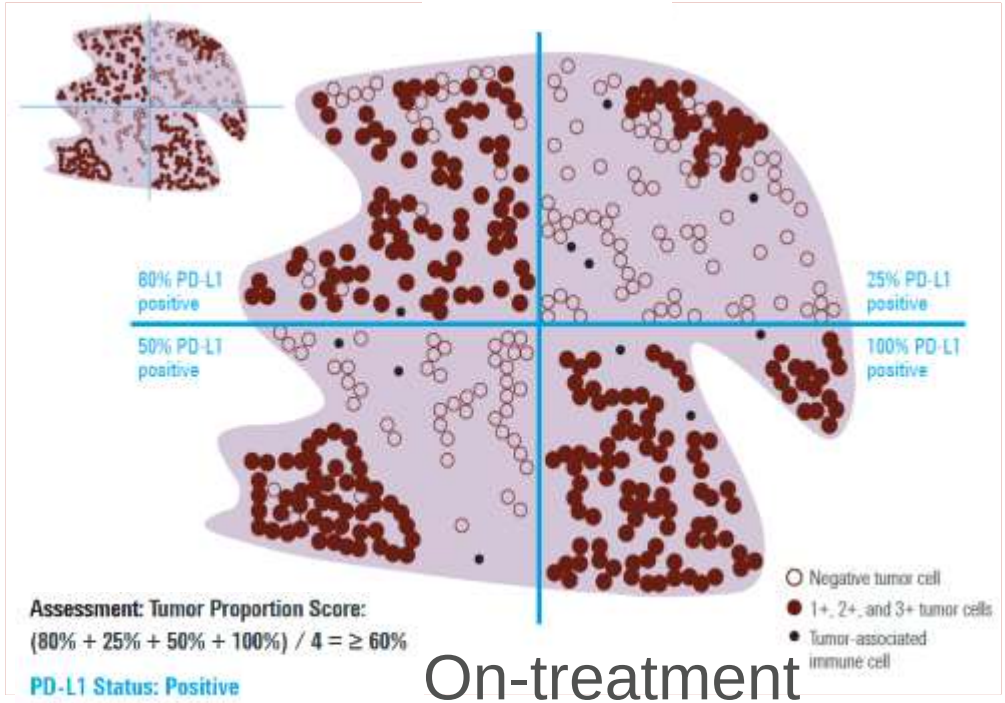
1. **Targeted therapy: new targets**
   - muts, fusions, CNVs
   - *driver variations*
   - *actionable variations*
   - immune checkpoint
2. **Tumor heterogeneity**
   - cancer biology
   - drug resistance
3. **Classification**
   - WHO & beyond
4. **Prognosis**





PD-L1 assessing for immunotherapy





Baseline

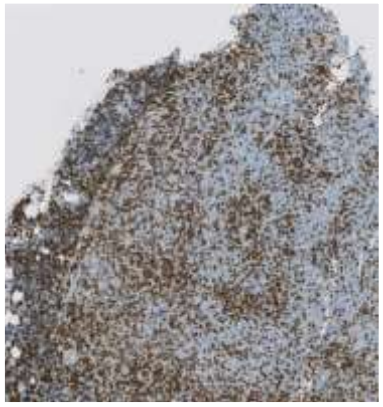
On-treatment

CD8 T cells

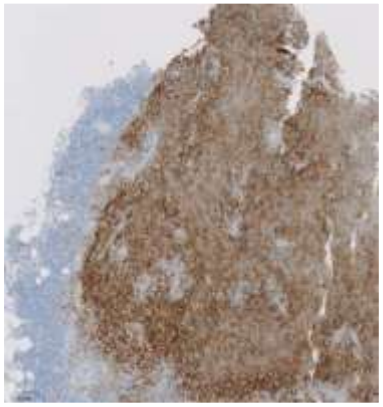
PD-L1

MPDL3280A (PD-L1 inhibitor)

CD8 T cells



PD-L1



PD-L1 assessing for immunotherapy

IASLC
INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER

IASLC 18TH WORLD CONFERENCE ON LUNG CANCER
October 15–18, 2017 | Yokohama, Japan
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Blueprint Phase 2 Team Members

15 countries **5 continents**

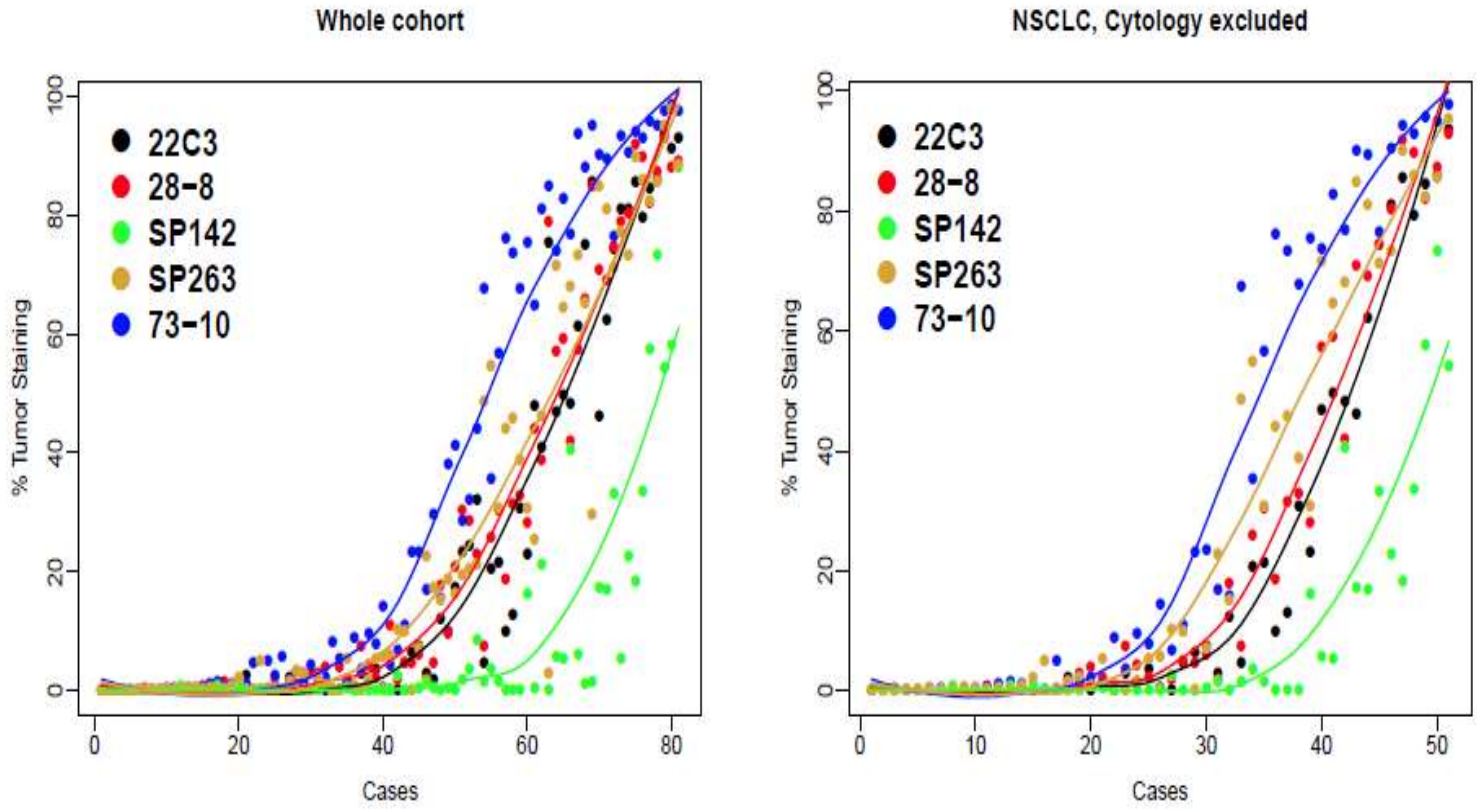
- M. S. Tsao (Toronto)
- M.-B. Beasley (New York)
- A. Borczuk (New York)
- A. Moreira (New York)
- J. Sauter (New York)
- W. D. Travis (New York)
- L. Chirieac (Boston)
- M. Mino-Kenudson (Boston)
- S. Dacic (Pittsburgh)
- I. Wistuba (Houston)
- F. R. Hirsch (Denver)
- H. Yu (Denver)
- M. Wynes (Denver)
- C. Poleri (Buenos Aires)

STATISTICS: M. Pintilie (Toronto)

- Y. Yatabe (Nagoya)
- M. Noguchi (Tokyo)
- K. M. Kerr (Aberdeen)
- A. G. Nicholson (London)
- S. Lantuejoul (Lyon)
- **G. Pelosi (Milan)**
- L. Bubendorf (Basel)
- J. Botling (Uppsula)
- E. Thunnissen (Amsterdam)
- M. Kockx (Antwerp)
- J.-H. Chung (Seoul)
- G. Chen (Shanghai)
- T.-Y. Chou (Taipei)
- P. Russell (Melbourne)

PD-L1 assessing for immunotherapy

Comparability among five assays on tumor cell staining



Each circle represents the mean of all scores (glass slide & digital combined)

PD-L1 assessing for immunotherapy

Moderate to strong reliability among all pathologists on tumor cell scoring

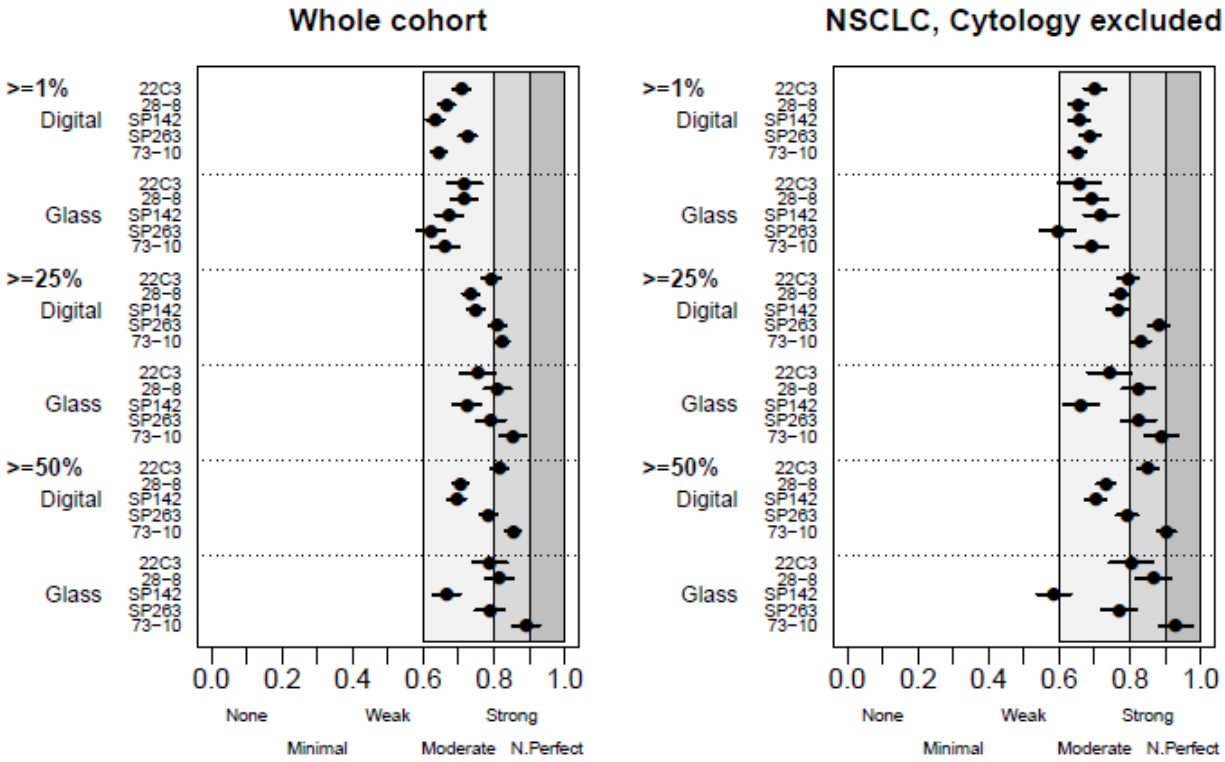
Fleiss Kappa Statistics[1]

>0.90: Near perfect

0.80-0.90: Strong

0.60-0.79: Moderate

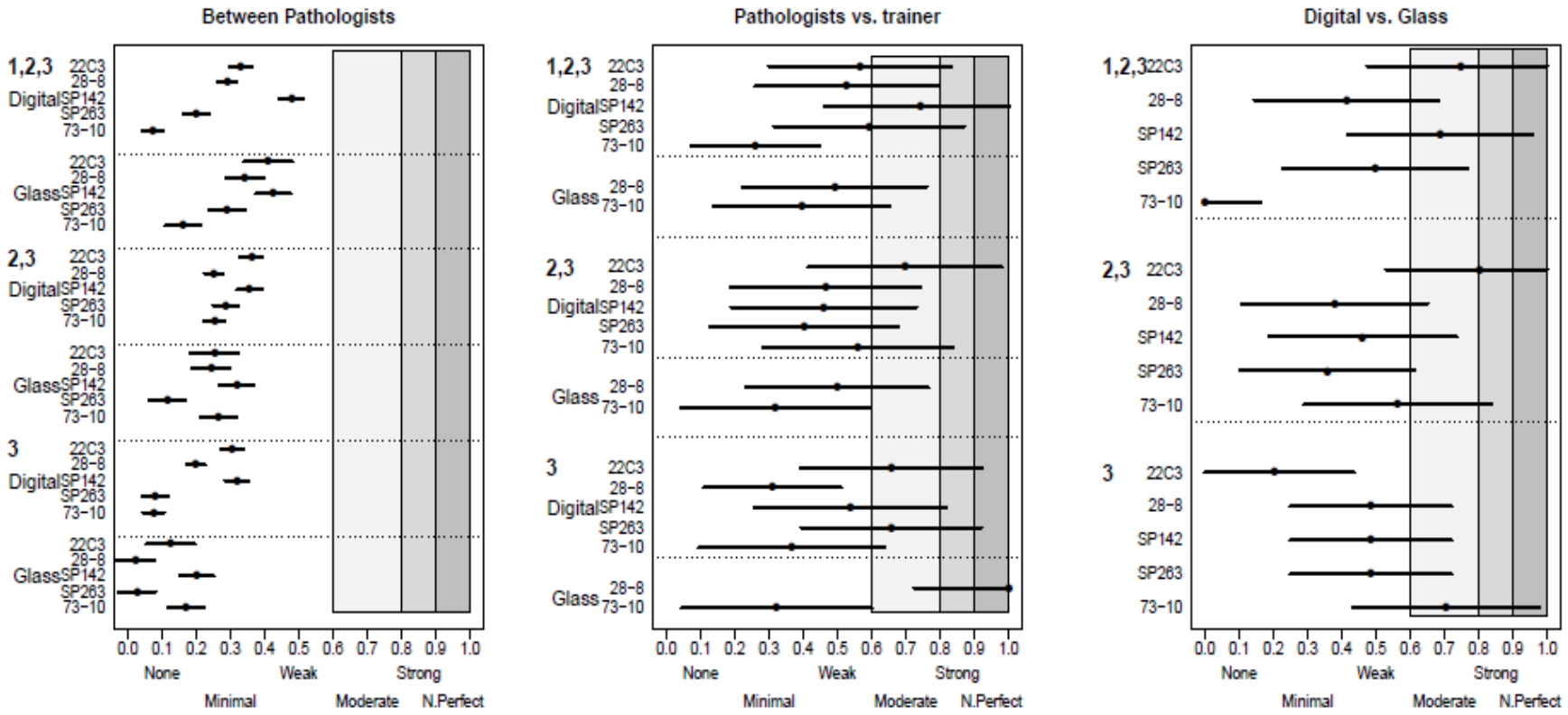
0.40-0.59: Weak



[1]McHugh ML. Biochemia Medica 2012;22:2
82

PD-L1 assessing for immunotherapy

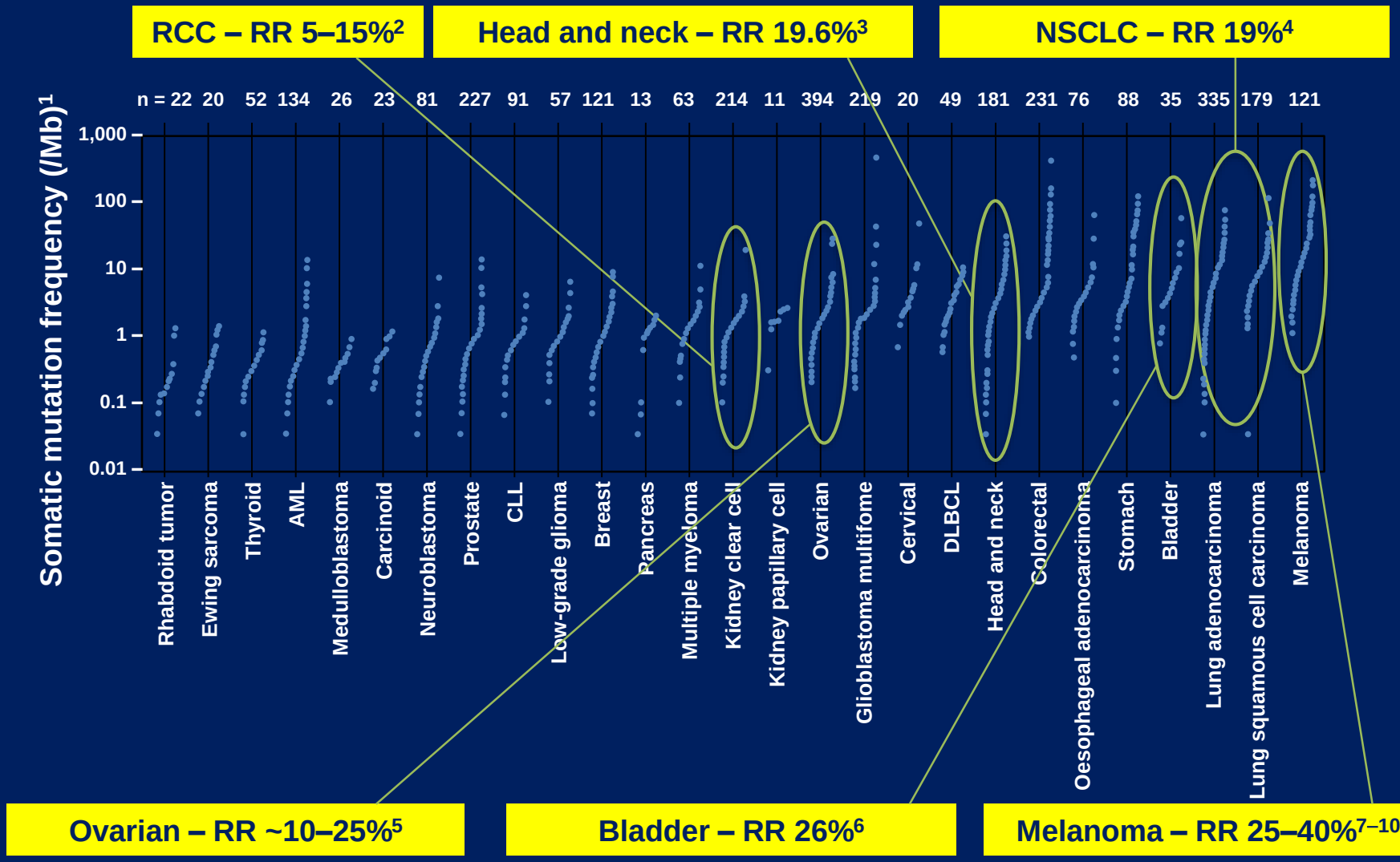
Poor reliability for immune cell scoring



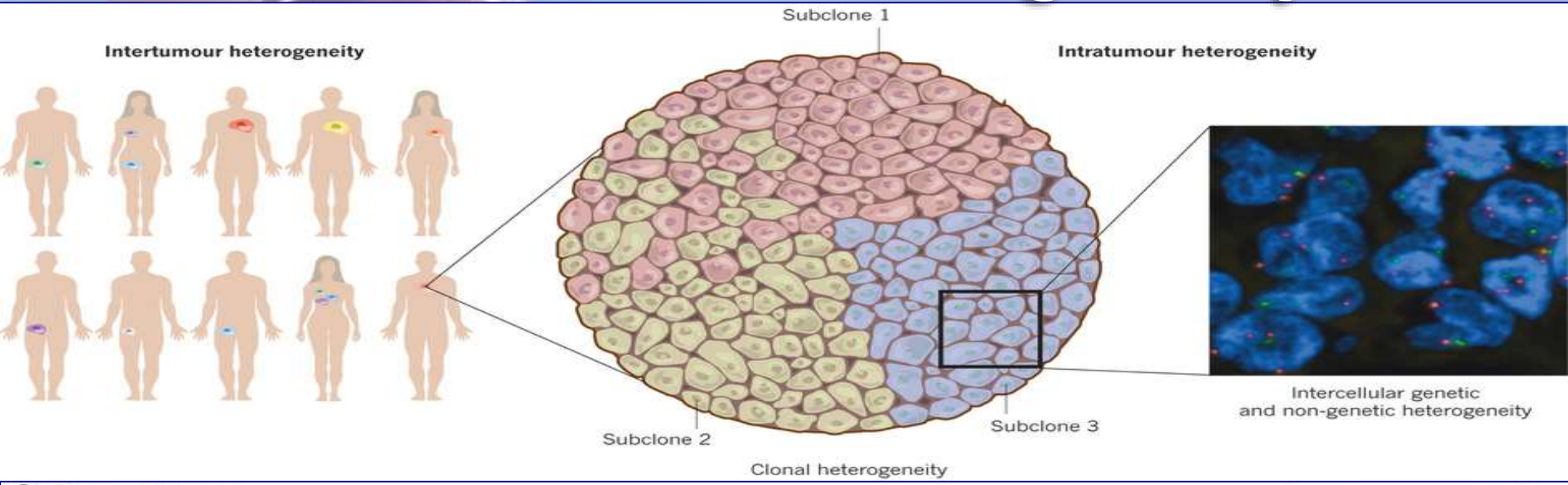
Fleiss Kappa Statistics **0.60-0.79: Moderate** **0.40-0.59: Weak** **0.21-0.39: Minimal**

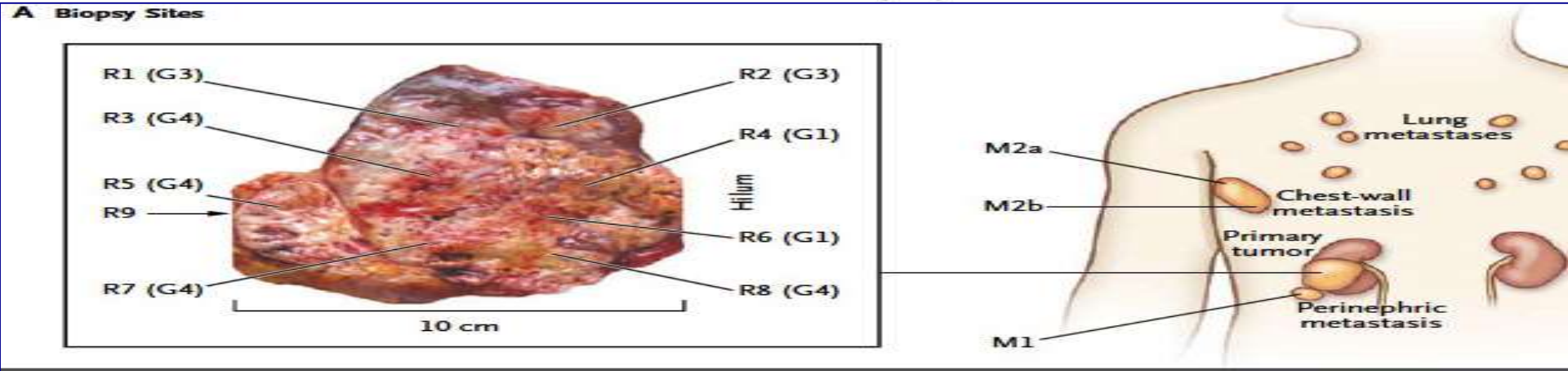
Tumor burden for immunotherapy

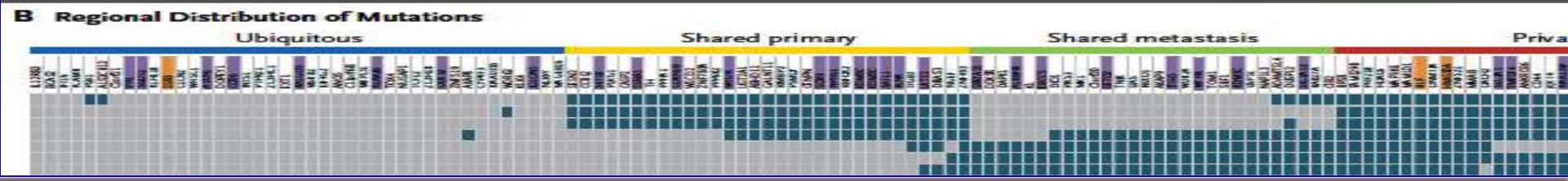
Mutation burden (WES, WGS, TNGS, mismatch repair deficiency)



Tumor molecular heterogeneity

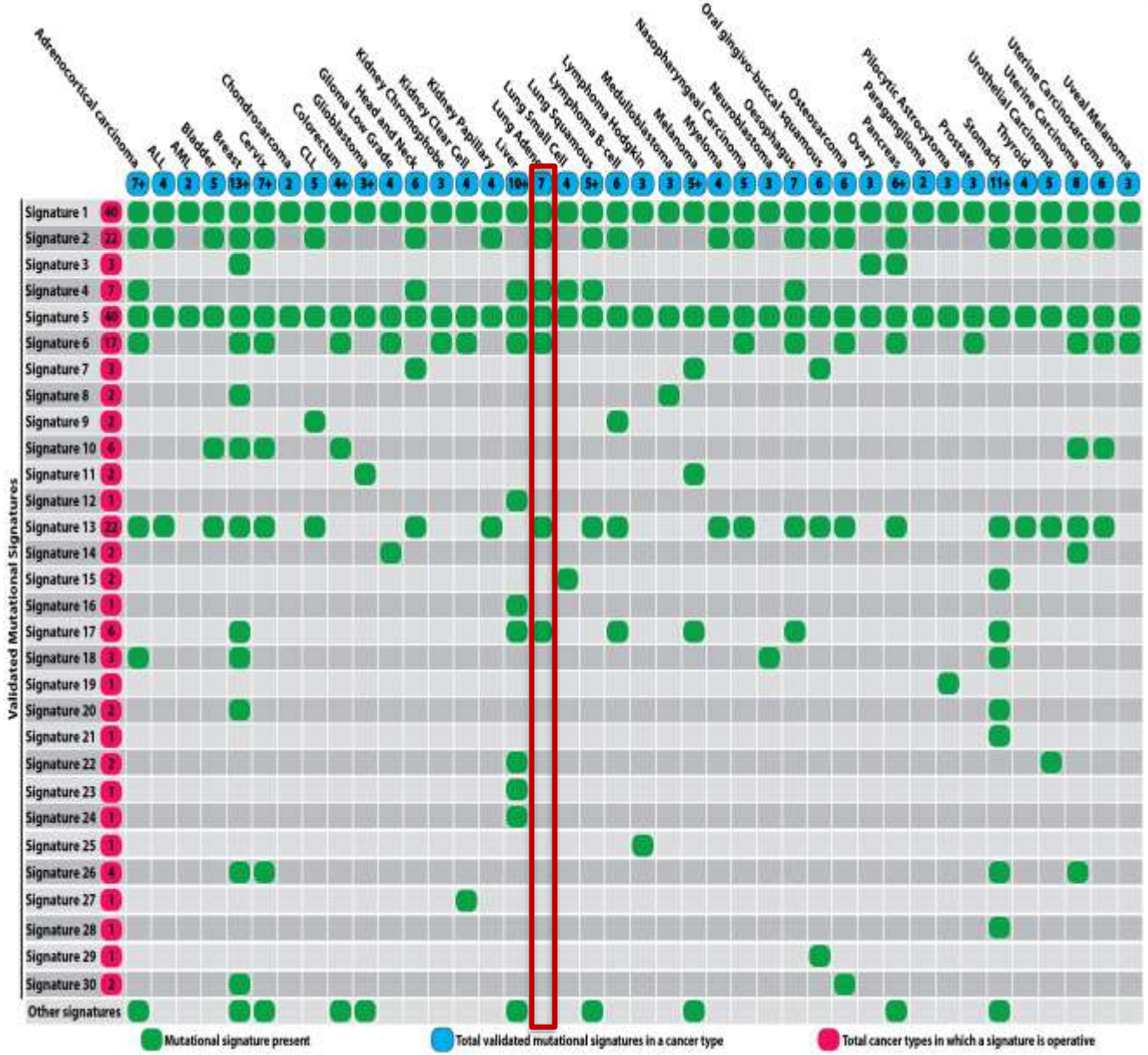






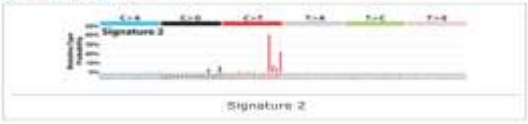
Tumor heterogeneity

COSMIC
Catalogue of somatic mutations in cancer

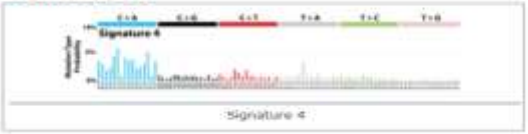


Signature 1 spontaneous deamination

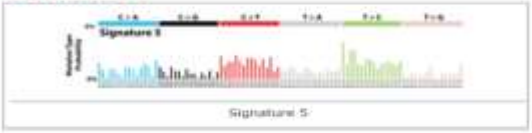
Signature 2 APOBEC activity



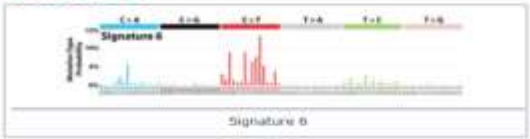
Signature 4 smoke-related DNA damage



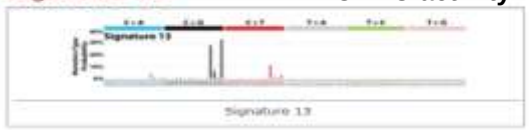
Signature 5 unknown



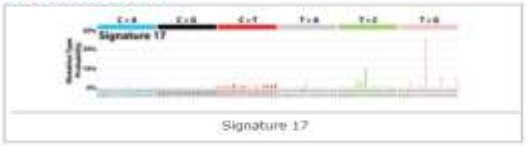
Signature 6 microsatellite instability



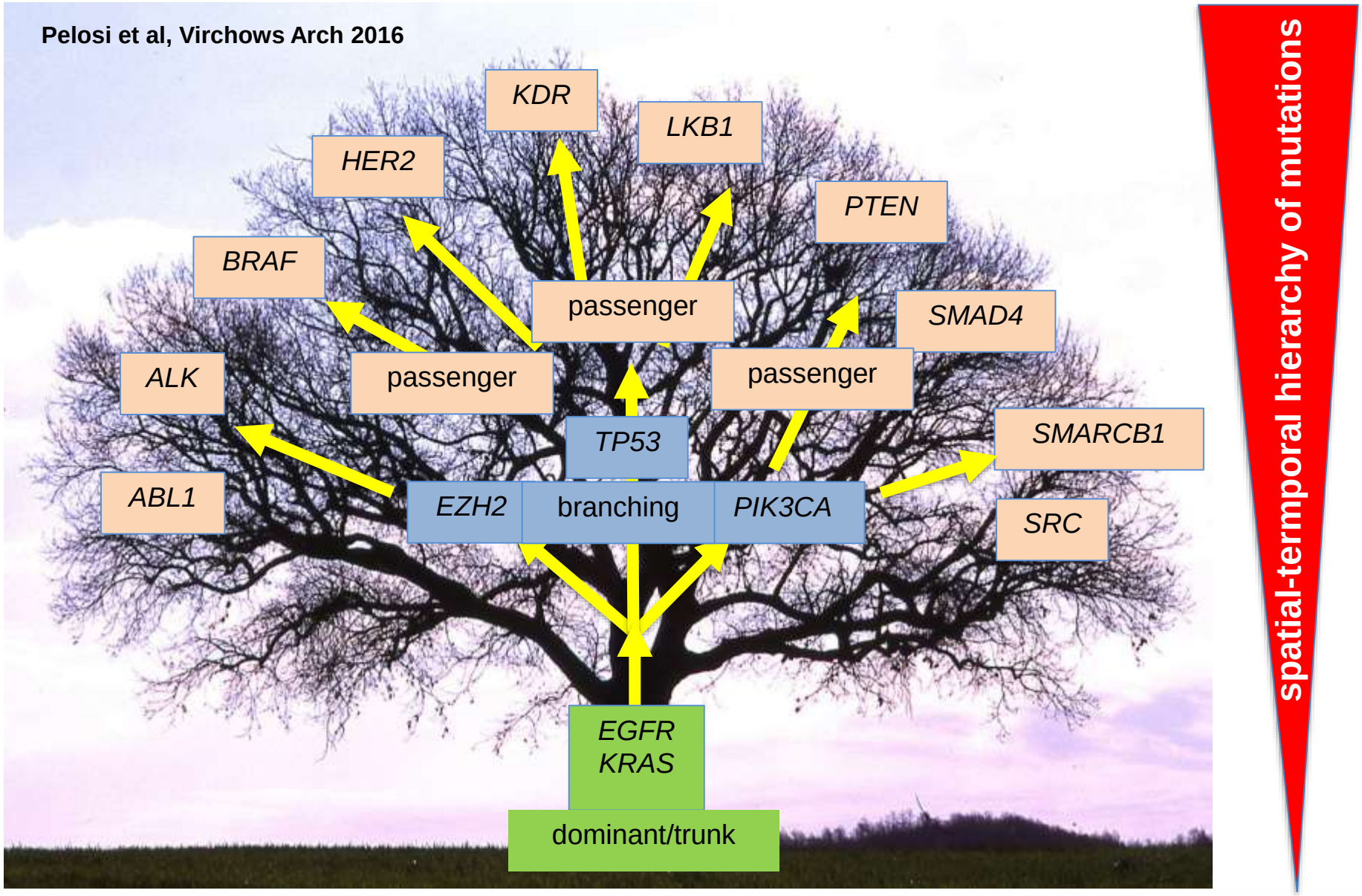
Signature 13 APOBEC activity



Signature 17 unknown



Tumor heterogeneity: cancer biology

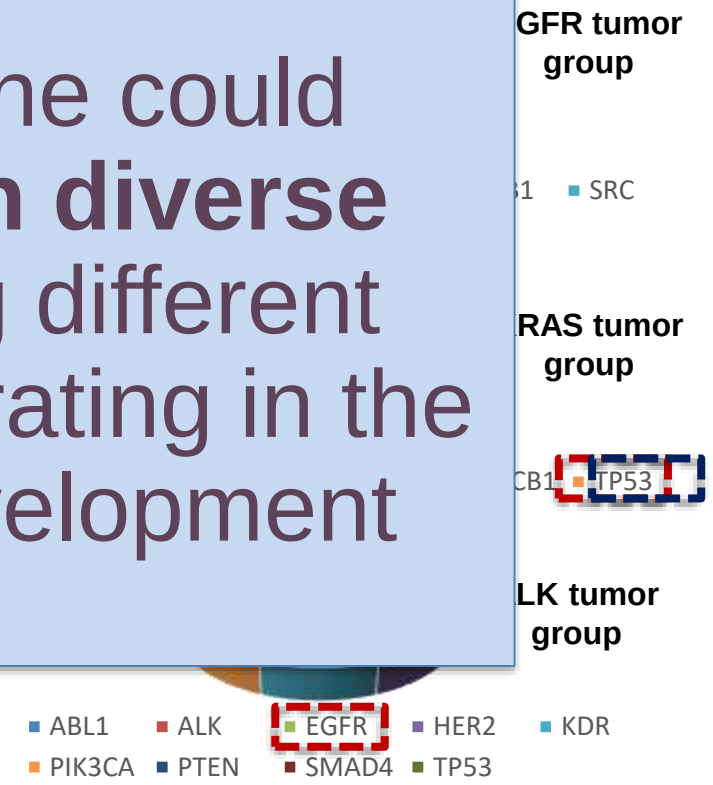


Tumor heterogeneity: cancer biology

Hierarchizing mutations

- ***EGF***
  mut
  in a
  alte
- ***TP5***
  pas
  mutated tumors

- The same gene could **diversely act in diverse ADC**, indicating different mechanisms operating in the lung cancer development



Pelosi et al, Virchows Arch 2016

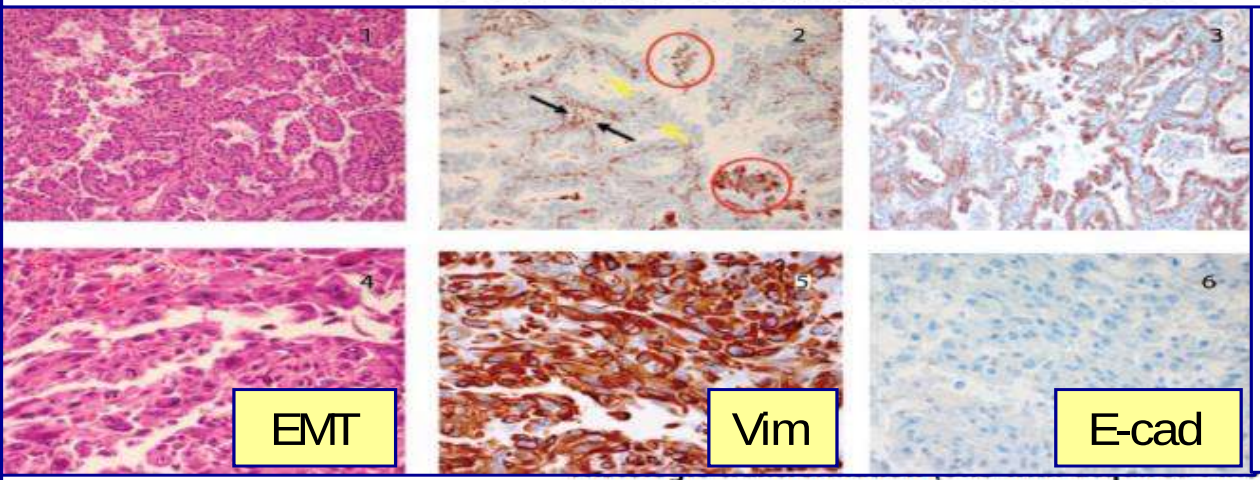
Tumor heterogeneity: resistance

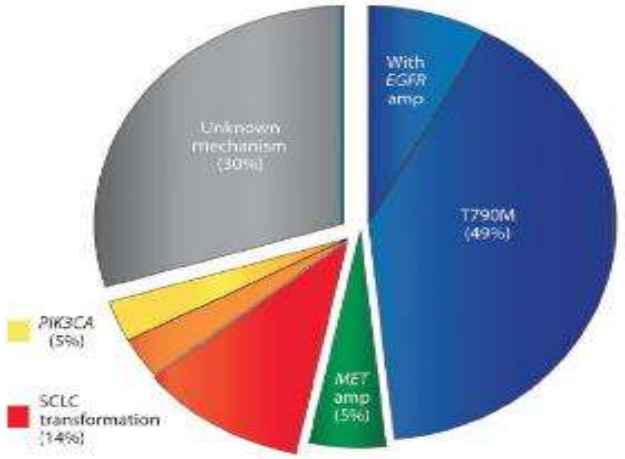
Science Translational Medicine
AAAS

Genotypic and Histological Evolution of Lung Cancers Acquiring Resistance to EGFR Inhibitors

Lecia V. Sequist, *et al.*

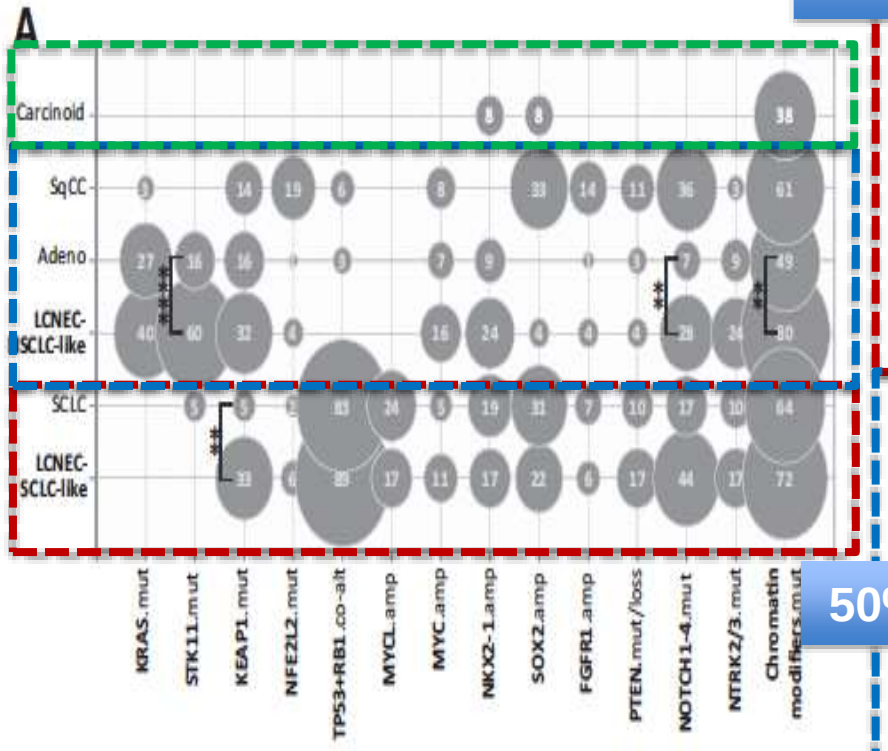
Sci Transl Med **3**, 75ra26 (2011);
DOI: 10.1126/scitranslmed.3002003



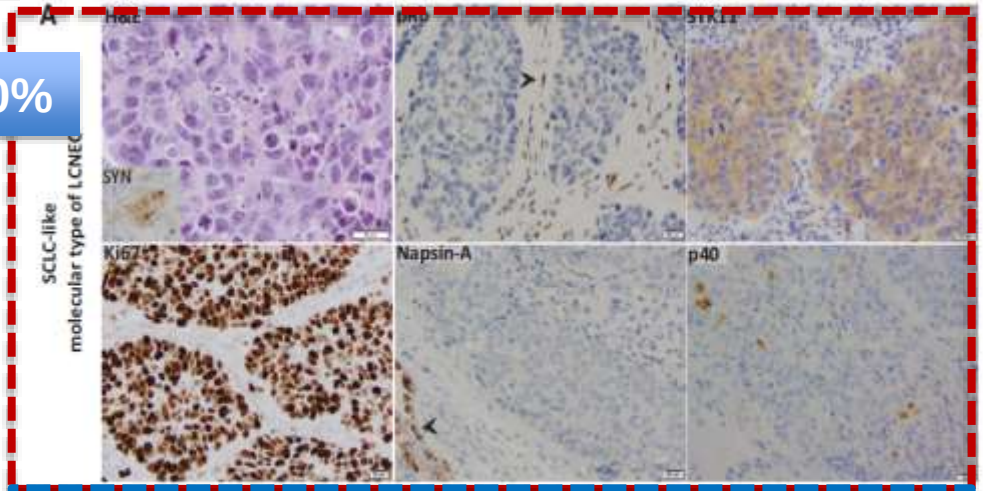


22	67	F	L858R	Adeno	SCLC transformation	Erlo (22 months)	On
23	54	F	Exon 19 del	Adeno	SCLC transformation	Erlo (3+ years)	On
24	56	F	L858R	Adeno	SCLC transformation, *PIK3CA*	Erlo (14 months)	On
25	40	F	Exon 19 del	Adeno	SCLC transformation	Erlo (2+ years)	Off (2 months)
26	61	F	L858R	Adeno	SCLC transformation	Erlo (18 months)	On
27	66	M	L858R	Adeno	EMT	Erlo (11 months)	On
28	59	M	Exon 20 ins‡	Adeno	EMT	Gef (11 months)	On
29	64	M	L858R	Adeno	Sarcomatoid CA, loss of β-*catenin*	Erlo (11 months)	Off (2 weeks)

Tumor heterogeneity: classification



40%



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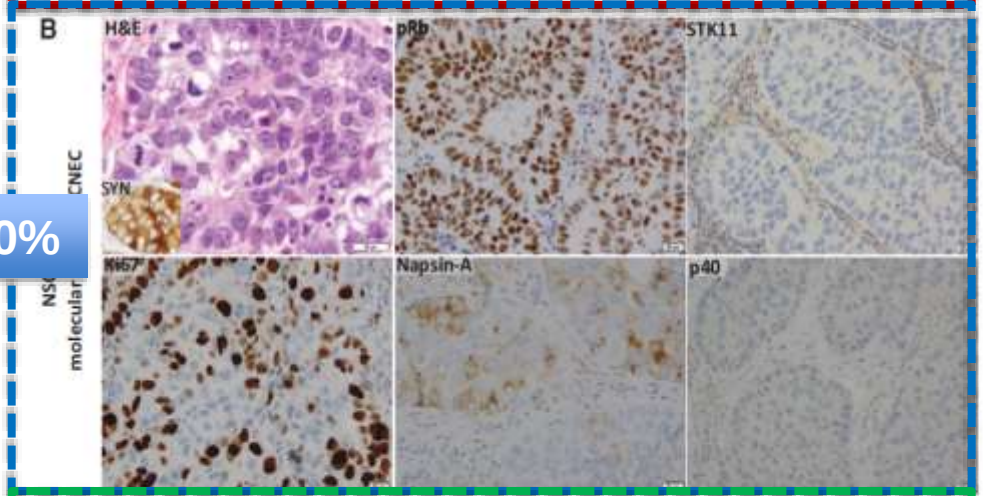

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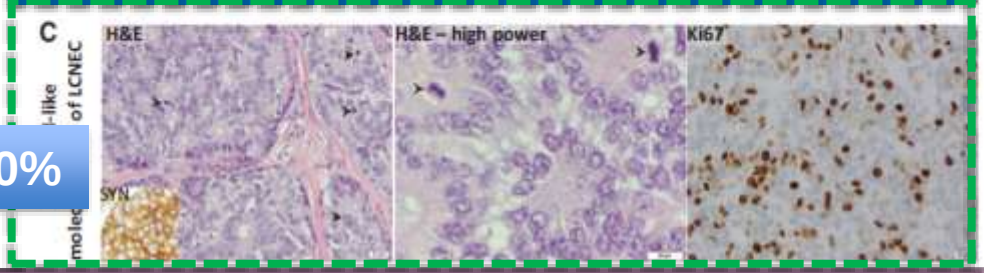


LCNEC is not one tumor only

Tumor heterogeneity: therapy

Genetic subtypes of large cell neuroendocrine carcinoma (LCNEC) to predict response to chemotherapy.

JOURNAL OF CLINICAL ONCOLOGY

DOI: 10.1200/JCO.2017.35.15_suppl.9061
Journal of Clinical Oncology 35, no. 15_suppl (May 2017) 9061-9061.

Jules Derks, Noémie Leblay, Robert Jan van Suylen, Erik Thunnissen, Michael den Bakker, Harry J.M. Groen, ...Egbert F. Smit, Ronald Damhuis, Esther van de Broek, Amélie Chabrier, Matthieu Foll, James McKay, Lynnette Fernandez-Cuesta, Ernst-Jan M. Speel, Anne-Marie C. Dingemans,

77 LCNEC
TNGS: TP53 (87%), RB1 (46%), STK11 (13%), KEAP1 (18%)
Co-mutation: TP53-RB1 (94%), STK11-KEAP1 (never RB1-STK11)

NSCLC-t: plat + gem/taxanes/pem
SCLC-t: plat + etoposide

RB1^{wt} → NSCLC-t vs. SCLC-t → 8.5 mo. vs 5.8 mo., p=0.05

without pemetrexed → 9.6 mo. vs 5.8 mo. p=0.026

RB1^{mut} → NSCLC-t vs. SCLC-t → no differences

SCLC-ct. **Conclusions:** In LCNEC with *RB1*^{wt}, NSCLC-ct correlates with a more favorable outcome compared to SCLC-ct. However, *RB1*^{mt} *LCNEC* treated with NSCLC-ct do similarly worse as SCLC-ct.Prospective studies should be initiated.

Molecular matters for therapy

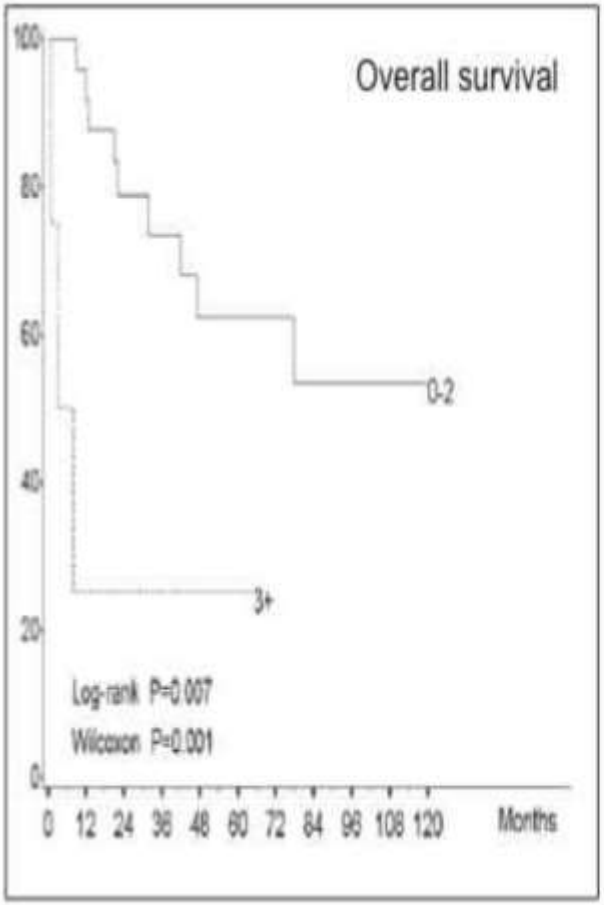
LCNEC not one tumor only!

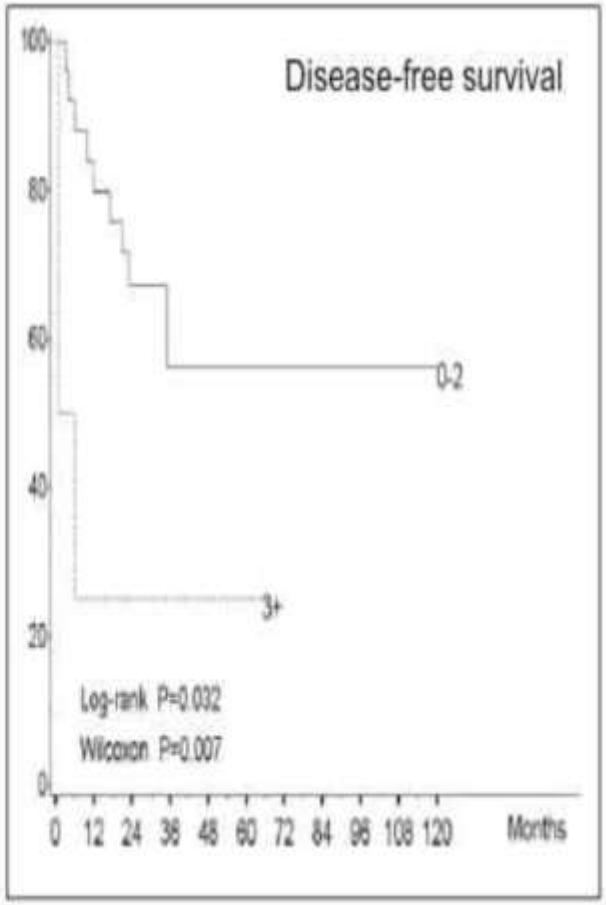
Tumor heterogeneity: prognosis

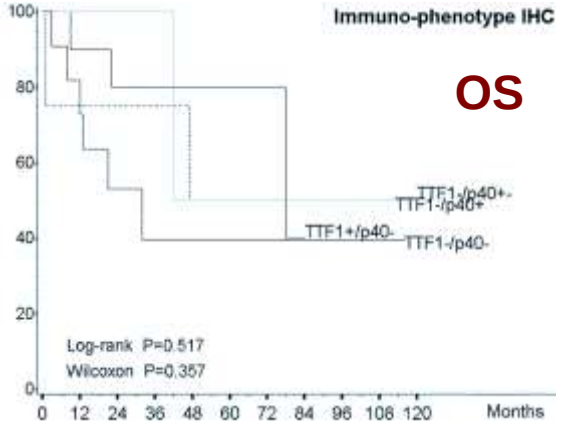
Dissecting Pulmonary Large-Cell Carcinoma by Targeted Next Generation Sequencing of Several Cancer Genes Pushes Genotypic–Phenotypic Correlations to Emerge

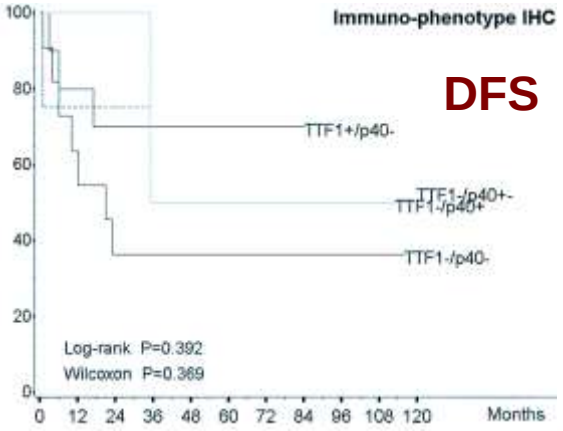
Giuseppe Pelosi, MD, MIAC,† Alessandra Fabbri, MD,* Mauro Papotti, MD,‡ Giulio Rossi, MD,§ Alberto Cavazza, MD,‖ Luisella Righi, MD,‡ Elena Tamborini, DSc,* Federica Perrone, DSc,* Giulio Settanni, DSc,* Adele Busico, DSc,* Maria Adele Testi, DSc,* Patrick Maisonneuve, Eng,¶ Filippo De Braud, MD,# Marina Garassino, MD,# Barbara Valeri, MD,* Angelica Sonzogni, MD,* and Ugo Pastorino, MD***

(*J Thorac Oncol.* 2015;XX: 00–00)









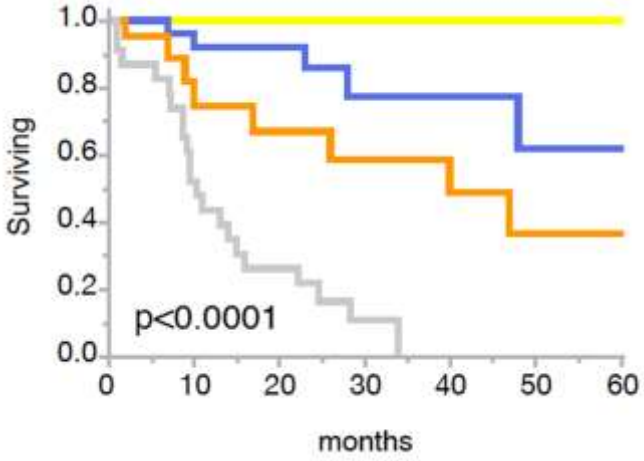
Tumor heterogeneity: pathogenesis

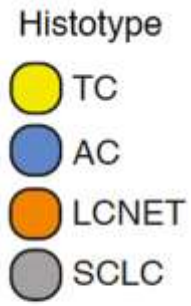
Virchows Archiv
https://doi.org/10.1007/s00428-018-2307-3

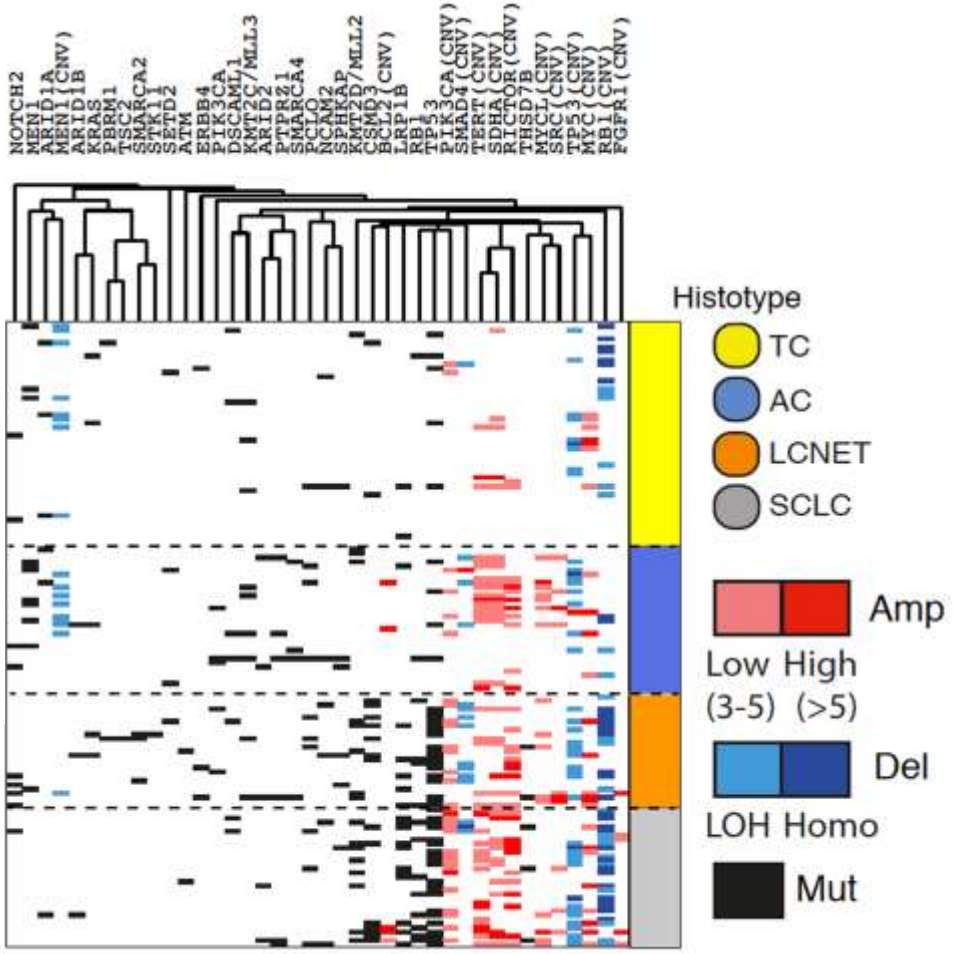
ORIGINAL ARTICLE

Most high-grade neuroendocrine tumours of the lung are likely to secondarily develop from pre-existing carcinoids: innovative findings skipping the current pathogenesis paradigm

Giuseppe Pelosi[1,2,3] · Fabrizio Bianchi[4] · Elisa Dama[4] · Michele Simbolo[5] · Andrea Mafficini[3] · Angelica Sonzogni[6] · Sara Pilotto[7] · Sergio Harari[8] · Mauro Papotti[9] · Marco Volante[10] · Gabriella Fontanini[11] · Luca Mastracci[12] · Adriana Albini[13] · Emilio Bria[7] · Fiorella Calabrese[14] · Aldo Scarpa[5]







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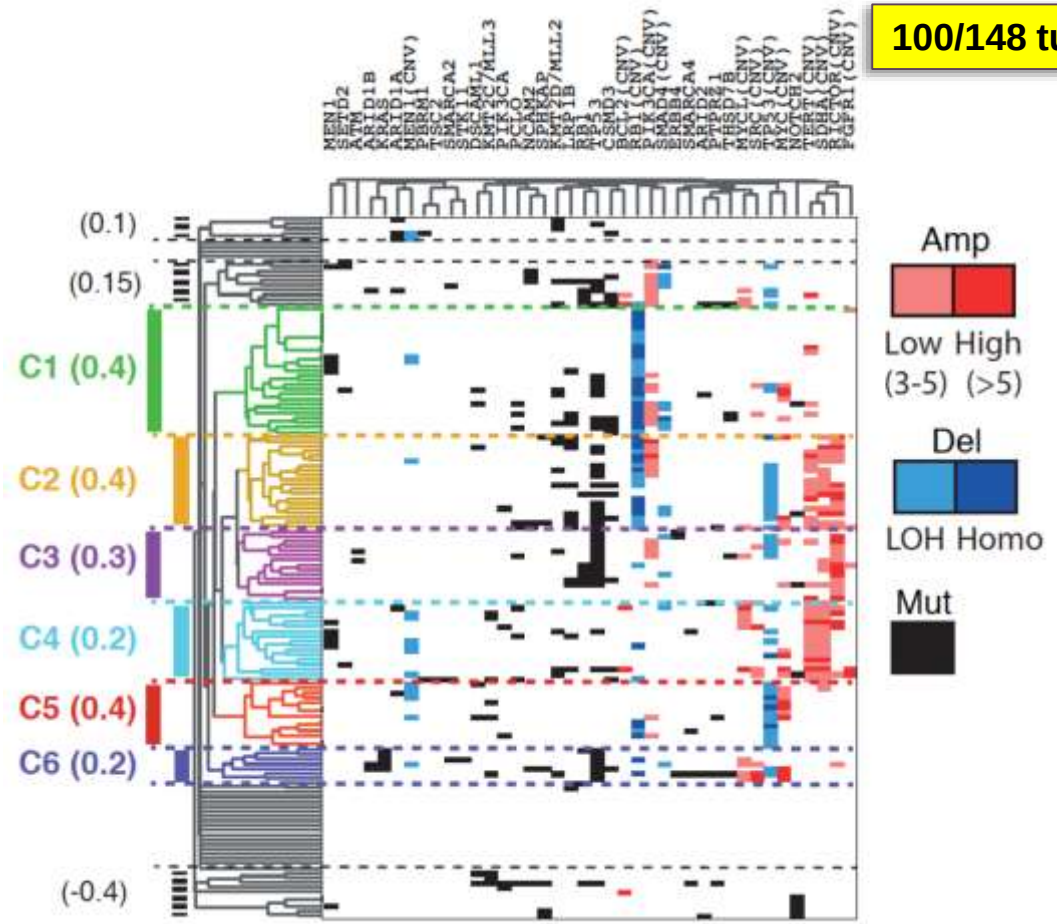
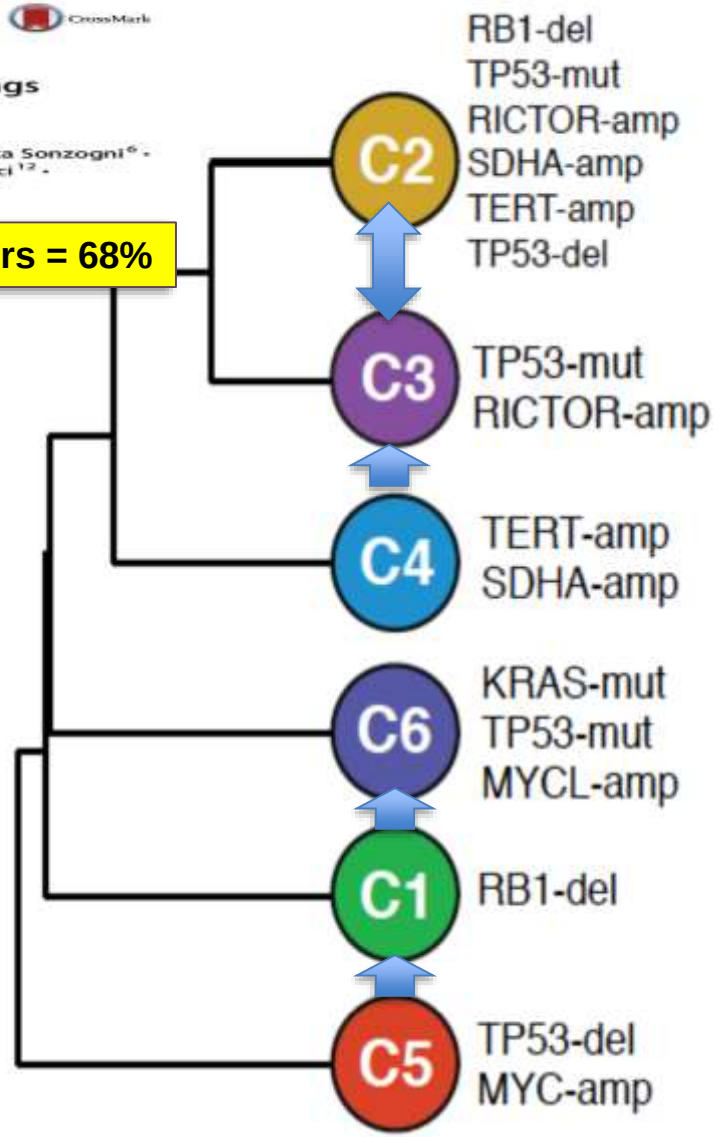
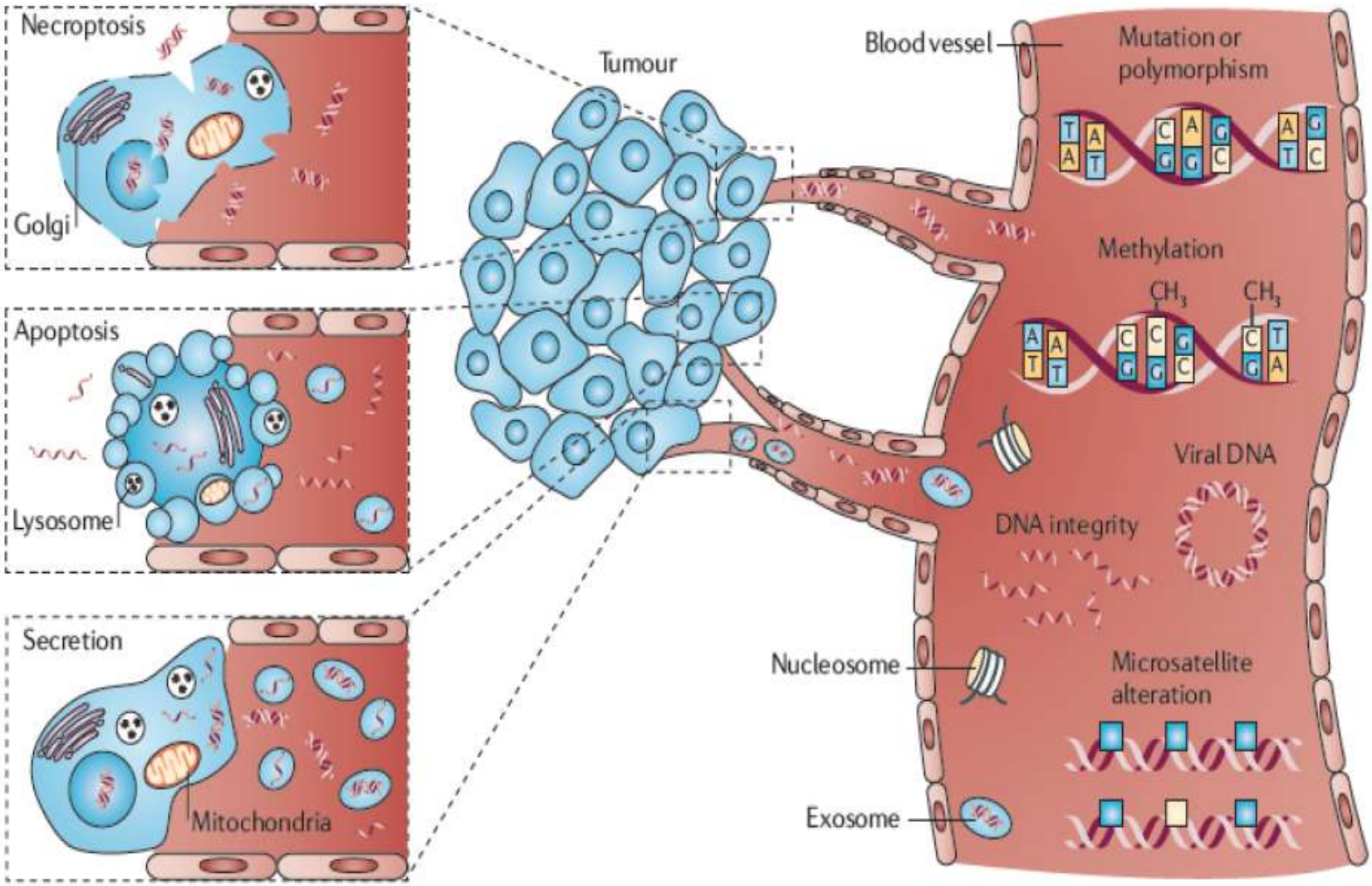


100/148 tumors = 68%



Liquid biopsy to reassess over time

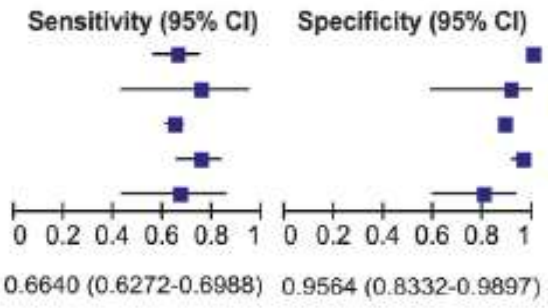


Schwarzenbach et al., Nat Rev Cancer 2011

cfDNA testing in liquid biopsy

- **R:** EGFR mutations when the tissue is an issue (also unwilling or unable patients)…but ***if negative*** try on tissue biopsy (also to exclude other resistance mechanisms)

Study	TP	FP	FN	TN	Detection System	Sensitivity (95% CI)	Specificity (95% CI)
Douillard 2014[242]	69	1	36	546	ARMs	0.66 [0.56, 0.75]	1.00 [0.99, 1.00]
Kukita 2013[234]	9	1	3	10	PNA/LNA clamp	0.75 [0.43, 0.95]	0.91 [0.59, 1.00]
Li 2014[243]	389	114	214	874	Multiple	0.65 [0.61, 0.68]	0.88 [0.86, 0.90]
Mok 2015[235]	72	6	24	136	allele-specific PCR	0.75 [0.65, 0.83]	0.96 [0.91, 0.98]
Oxnard 2014[232]	14	5	7	20	ddPCR	0.67 [0.43, 0.85]	0.80 [0.59, 0.93]



Sensitivity 60-80%; specificity 80-95%

- **ECO:** Identifying EGFR T790M mutation in lung ADC patients with progression or secondary clinical resistance to EGFR-TKI

- **No R:** cfDNA & CTC cannot be used for diagnosis of primary lung cancer; CTC cannot be used for the identification of EGFR or other mutations or EGFR T790M

R: recommendation; ECO: expert consensus opinion

Lindeman, JTO 2018

Summing up..

- Subtyping, essential
- Multiplexed testing, by far preferable to stand-alone genes
- Molecular classification for clinical handling, classification and prognosis
- cfDNA, a potential standard in EGFR TKI-treated lung cancer patients