Molecular pathology and lung cancer

PNEUMOLOGIA 2018

Milano, 14 – 16 giugno 2018 · Centro Congressi Palazzo delle Stelline

MINICORSO | Giovedì, 14 giugno 2018

TUMORE POLMONARE E DINTORNI

Coordinatori: *Vittorio Bedini (Milano), Ornella Gottardi (Milano)*
Moderatori: *Vittorio Bedini (Milano), Ornella Gottardi (Milano)*

14.00 - 14.20	La prevenzione: il fumo *Silvano Gallus (Milano)*
14.20 - 14.40	Biologia molecolare e tumori polmonari *Giuseppe Pelosi (Milano)*
14.40 - 15.00	Le nuove terapie del tumore polmonare *Marina Garassino (Milano)*
15.00 - 15.20	Discussione
15.20 - 15.40	La chirurgia dell'esofago *Vittorio Bedini (Milano)*
15.40 - 16.00	La chirurgia del timo *Federico Rea (Padova)*
16.00 - 16.20	La chirurgia polmonare negli stadi localmente avanzati *Ugo Pastorino (Milano)*
16.20 - 16.40	Le tecniche mini-invasive nel cancro del polmone *Lorenzo Spaggiari (Milano)*
16.40 - 17.00	Discussione

Giuseppe Pelosi

University of Milan & IRCCS Multimedica, Milan

UNIVERSITAS STUDIORUM MEDIOLANENSIS

Gruppo MultiMedica

Fondazione MultiMedica ONLUS

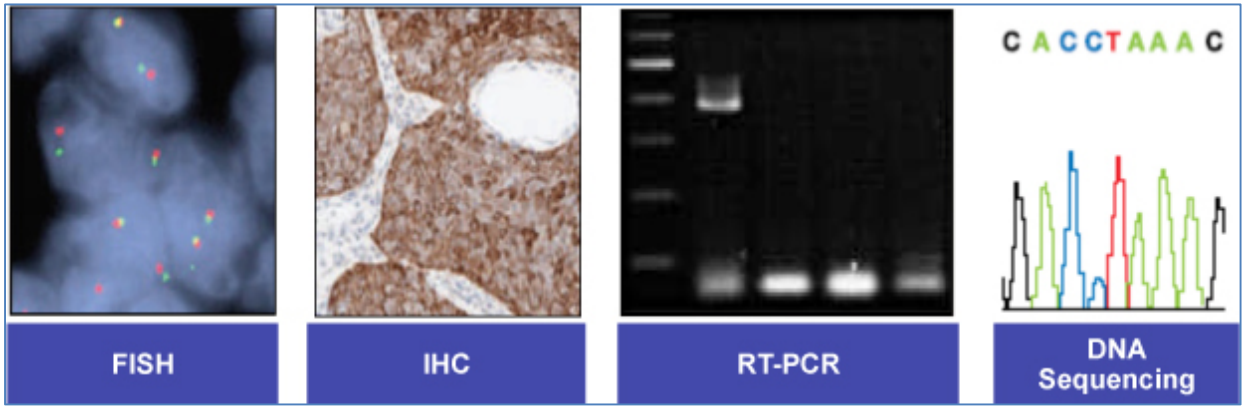
The issue of molecular pathology

Emerging discipline within Pathology focusing on disease study and diagnosis through molecular investigation of organs, tissues or bodily fluids

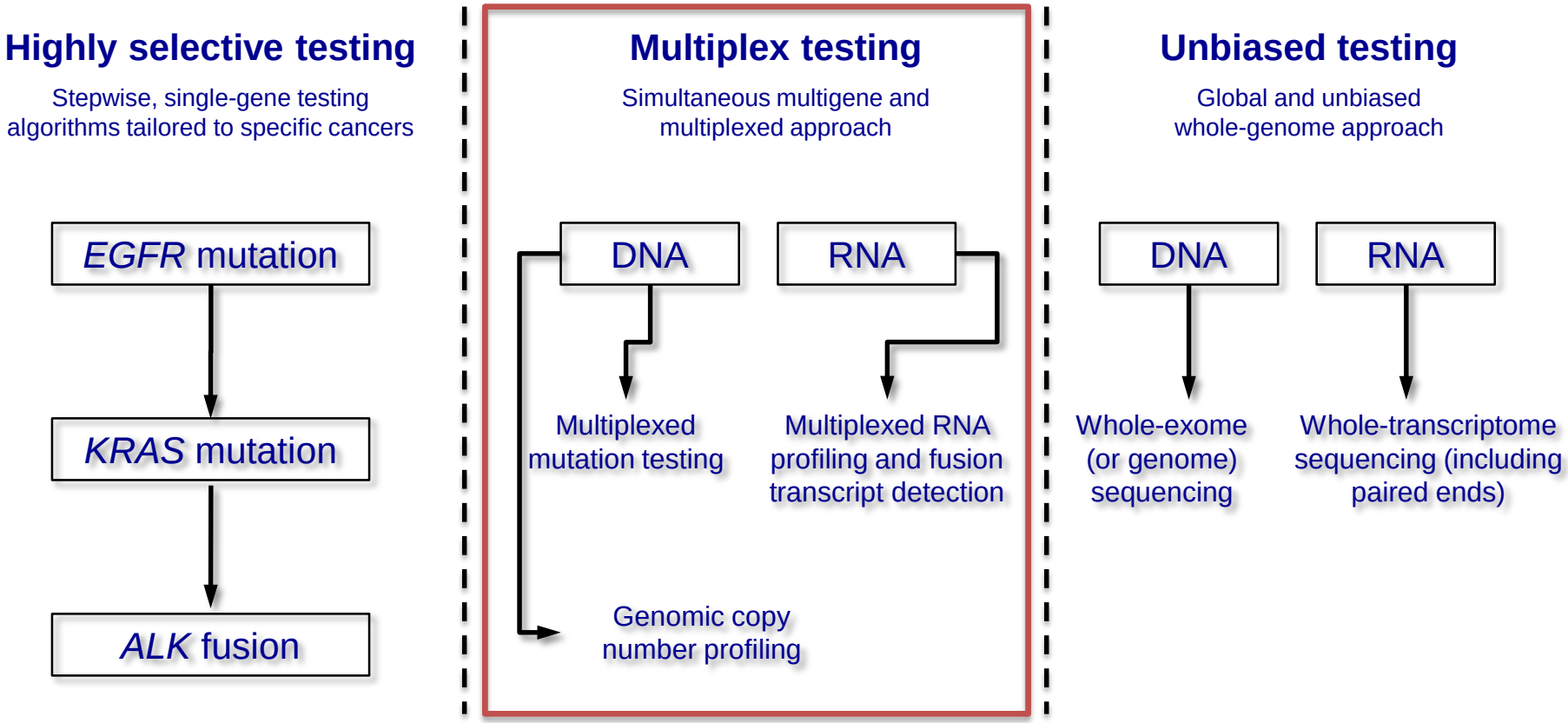
Harris et al, Nat Rev Clin Oncol 2010

Molecular biomarker testing

- **ISH:** amplification, gene copy gain, gene deletion, translocation (break-apart ISH), BISH (morphology), mRNA content
- **IHC:** cellular antigens (nucleus, membrane, cytoplasm)phosphorylated substrates (morphology is maintained)
- **RT-PCR, real-time PCR:** fusion transcripts, mutations, mRNA levels, also in biological fluids and circulating cancer cells
- **DNA/RNA sequencing:** mutations, fusion genes, GEP
- **Epigenetics:** hypermethylation, acethylation



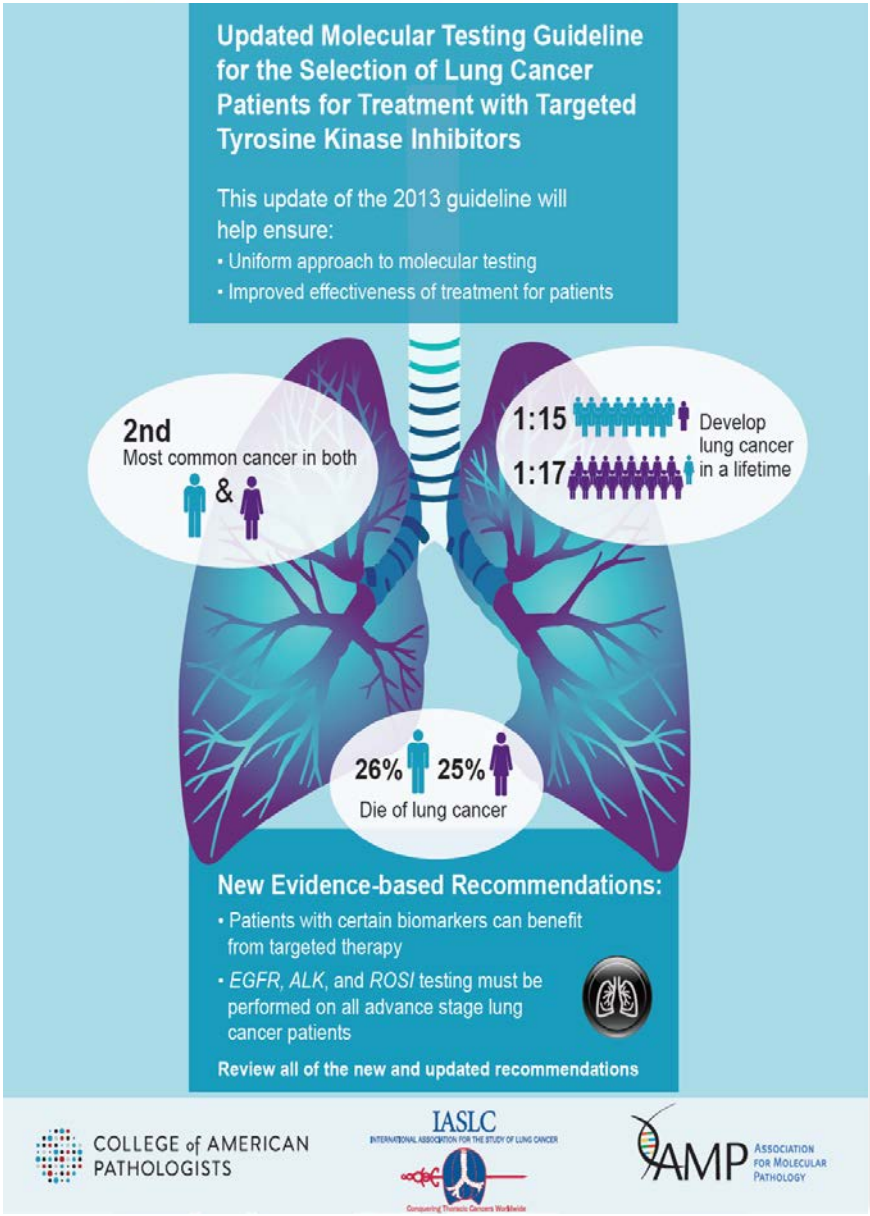
Molecular diagnostics



Present → Future

Taylor BS & Ladanyi M – J Pathol 2011

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

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]

- **Subtyping**
- *Oncogene addiction*
  - EGFR, ALK, ROS1 ☛ stand-alone gene;
  - HER2, MET, BRAF, KRAS, RET ☛ NGS panel
- *Immunohistochemistry for ALK/ROS1*
- *5% sensitivity assay for EGFR T790M*
- *cfDNA for targetable mutations*
  - when the tissue is an issue
- *Immunotherapy markers (PD-L1)*

Lindeman et al, JTO 2018;13:323

Advanced lung cancer (IIIB – IV)

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

Linee guida

NEOPLASIE DEL POLMONE

Edizione 2017

Aggiornamento 27 ottobre 2017

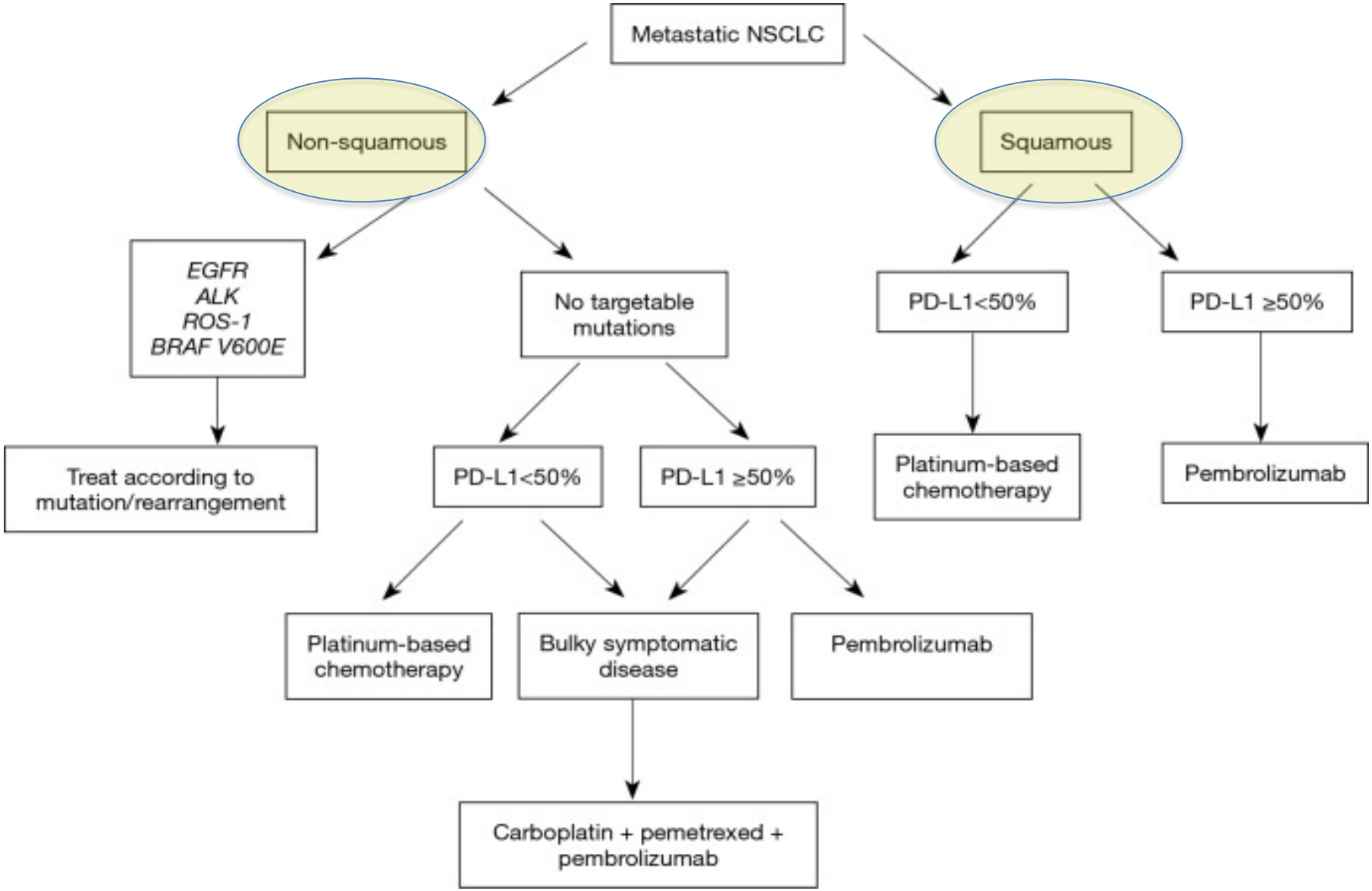
No oncogene addiction

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

Aiom

Associazione Italiana di Oncologia Medica

Advanced lung cancer (IIIB – IV)



Ernani, JTD 2018;10(S3):S412-S421

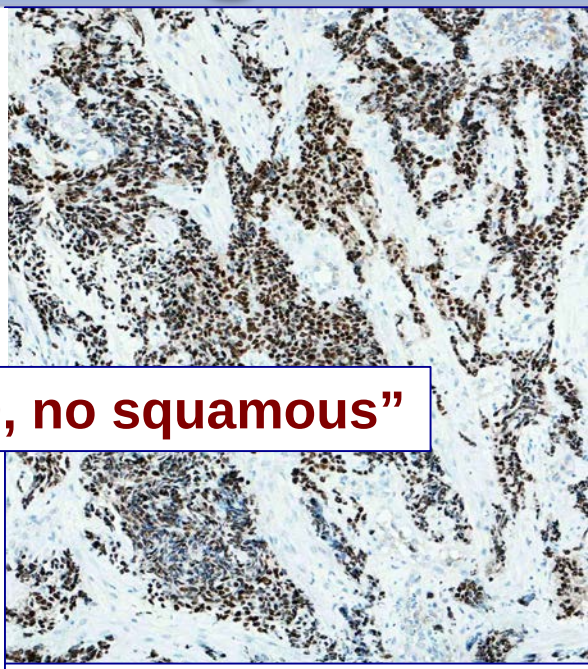
Minimalist subtyping to strategize

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

International Journal of Surgical Pathology
XX(X) 1–11

DOI: 10.1177/1066896913476750
ijsp.sagepub.com
SAGE

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)

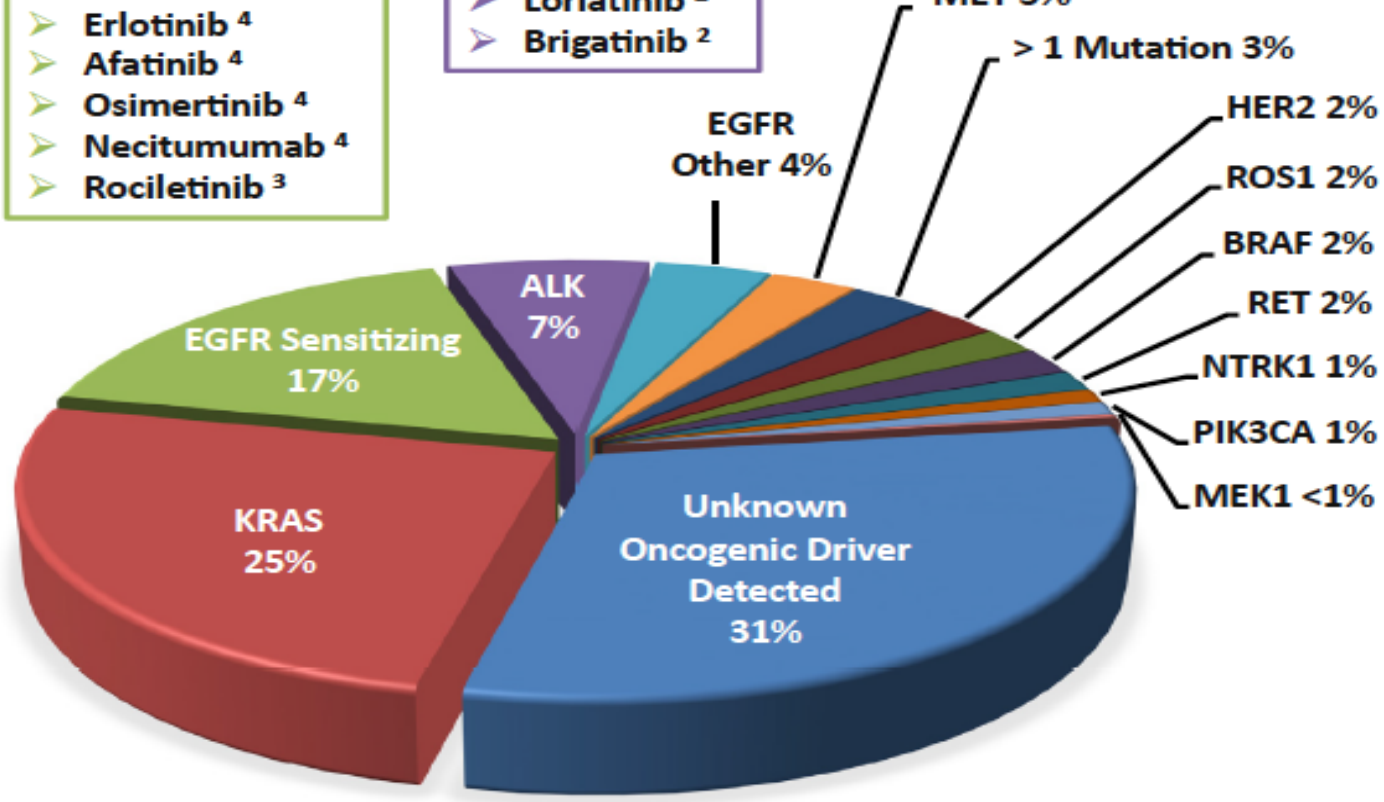
HS ≤10 negative category (n=106)	HS = 11-50 1+ category (n=1)	HS = 51-100 2+ category (n=3)	HS >100 3+ category (n=36)
AD (n=71)	AD (n=1)	ADSQC (n=3)#	SQC (n=27)
PLC-AD (n=11) CS-AD (n=2)			B-LCC (n=3)
SCLC (n=10) LCNEC (n=5) Carcinoid (n=2)			PLC-SQC (n=2)**
MEM (n=3)			ADSQC (n=2)*
			SGTT (n=2)
			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 lineage	n = 126	n = 2	n = 0	n = 40	<.00001
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	

Assessing molecular landscape



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	3 -Phase III
2 - Phase II	4 - Approved

Tsao et al, J Thorac Oncol 2016

Multiplex testing

Current Gene List†

Entire coding sequence (base substitutions, indels, copy number alterations).

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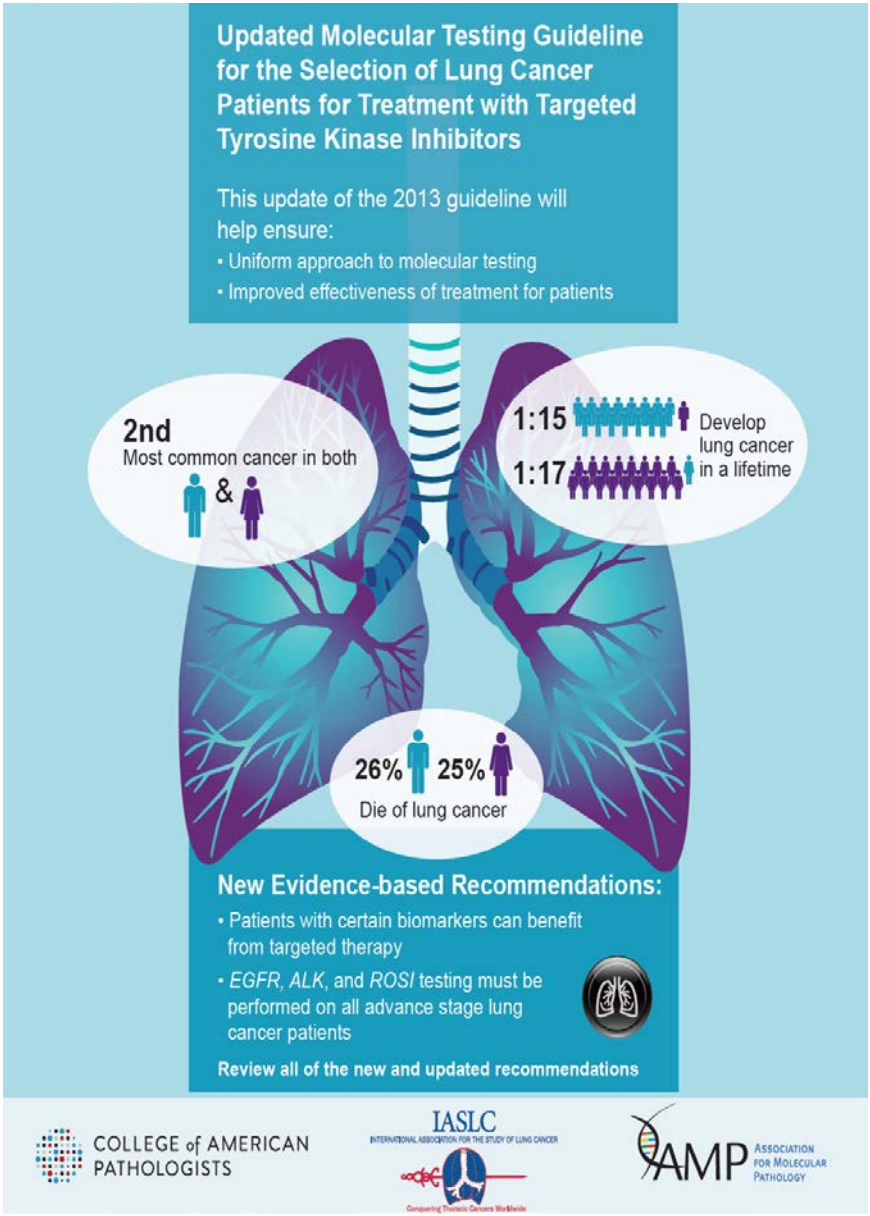
ABL1	*ABL2*	*ACVR1B*	*AKT1*	*AKT2*	*AKT3*	*ALK*	*AMER1 (FAM123B)*	*APC*
AR	*ARAF*	*ARFRP1*	*ARID1A*	*ARID1B*	*ARID2*	*ASXL1*	*ATM*	*ATR*
ATRX	*AURKA*	*AURKB*	*AXIN1*	*AXL*	*BAP1*	*BARD1*	*BCL2*	*BCL2L1*
BCL2L2	*BCL6*	*BCOR*	*BCORL1*	*BLM*	*BRAF*	*BRCA1*	*BRCA2*	*BRD4*
BRIP1	*BTG1*	*BTK*	*C11orf30 (EMSY)*	*CARD11*	*CBFB*	*CBL*	*CCND1*	*CCND2*
CCND3	*CCNE1*	*CD274 (PD-L1)*	*CD79A*	*CD79B*	*CDC73*	*CDH1*	*CDK12*	*CDK4*
CDK6	*CDK8*	*CDKN1A*	*CDKN1B*	*CDKN2A*	*CDKN2B*	*CDKN2C*	*CEBPA*	*CHD2*
CHD4	*CHEK1*	*CHEK2*	*CIC*	*CREBBP*	*CRKL*	*CRLF2*	*CSF1R*	*CTCF*
CTNNA1	*CTNNB1*	*CUL3*	*CYLD*	*DAXX*	*DDR2*	*DICER1*	*DNMT3A*	*DOT1L*
EGFR	*EP300*	*EPHA3*	*EPHA5*	*EPHA7*	*EPHB1*	*ERBB2*	*ERBB3*	*ERBB4*
ERG	*ERRFI1*	*ESR1*	*EZH2*	*FAM46C*	*FANCA*	*FANCC*	*FANCD2*	*FANCE*
FANCF	*FANCG*	*FANCL*	*FAS*	*FAT1*	*FBXW7*	*FGF10*	*FGF14*	*FGF19*
FGF23	*FGF3*	*FGF4*	*FGF6*	*FGFR1*	*FGFR2*	*FGFR3*	*FGFR4*	*FH*
FLCN	*FLT1*	*FLT3*	*FLT4*	*FOXL2*	*FOXP1*	*FRS2*	*FUBP1*	*GABRA6*
GATA1	*GATA2*	*GATA3*	*GATA4*	*GATA6*	*GID4 (C17orf39)*	*GLI1*	*GNA11*	*GNA13*
GNAQ	*GNAS*	*GPR124*	*GRIN2A*	*GRM3*	*GSK3B*	*H3F3A*	*HGF*	*HNF1A*
HRAS	*HSD3B1*	*HSP90AA1*	*IDH1*	*IDH2*	*IGF1R*	*IGF2*	*IKBKE*	*IKZF1*
IL7R	*INHBA*	*INPP4B*	*IRF2*	*IRF4*	*IRS2*	*JAK1*	*JAK2*	*JAK3*
JUN	*KAT6A (MYST3)*	*KDM5A*	*KDM5C*	*KDM6A*	*KDR*	*KEAP1*	*KEL*	*KIT*
KLHL6	*KMT2A (MLL)*	*KMT2C (MLL3)*	*KMT2D (MLL2)*	*KRAS*	*LMO1*	*LRP1B*	*LYN*	*LZTR1*
MAGI2	*MAP2K1 (MEK1)*	*MAP2K2 (MEK2)*	*MAP2K4*	*MAP3K1*	*MCL1*	*MDM2*	*MDM4*	*MED12*
MEF2B	*MEN1*	*MET*	*MITF*	*MLH1*	*MPL*	*MRE11A*	*MSH2*	*MSH6*
MTOR	*MUTYH*	*MYC*	*MYCL (MYCL1)*	*MYCN*	*MYD88*	*NF1*	*NF2*	*NFE2L2*
NFKBIA	*NKX2-1*	*NOTCH1*	*NOTCH2*	*NOTCH3*	*NPM1*	*NRAS*	*NSD1*	*NTRK1*
NTRK2	*NTRK3*	*NUP93*	*PAK3*	*PALB2*	*PARK2*	*PAX5*	*PBRM1*	*PDCD1LG2 (PD-L2)*
PDGFRA	*PDGFRB*	*PDK1*	*PIK3C2B*	*PIK3CA*	*PIK3CB*	*PIK3CG*	*PIK3R1*	*PIK3R2*
PLCG2	*PMS2*	*POLD1*	*POLE*	*PPP2R1A*	*PRDM1*	*PREX2*	*PRKAR1A*	*PRKCI*
PRKDC	*PRSS8*	*PTCH1*	*PTEN*	*PTPN11*	*QKI*	*RAC1*	*RAD50*	*RAD51*
RAF1	*RANBP2*	*RARA*	*RB1*	*RBM10*	*RET*	*RICTOR*	*RNF43*	*ROS1*
RPTOR	*RUNX1*	*RUNX1T1*	*SDHA*	*SDHB*	*SDHC*	*SDHD*	*SETD2*	*SF3B1*
SLIT2	*SMAD2*	*SMAD3*	*SMAD4*	*SMARCA4*	*SMARCB1*	*SMO*	*SNCAIP*	*SOCS1*
SOX10	*SOX2*	*SOX9*	*SPEN*	*SPOP*	*SPTA1*	*SRC*	*STAG2*	*STAT3*
STAT4	*STK11*	*SUFU*	*SYK*	*TAF1*	*TBX3*	*TERC*	*TERT (Promoter only)*	*TET2*
TGFBR2	*TNFAIP3*	*TNFRSF14*	*TOP1*	*TOP2A*	*TP53*	*TSC1*	*TSC2*	*TSHR*
U2AF1	*VEGFA*	*VHL*	*WISP3*	*WT1*	*XPO1*	*ZBTB2*	*ZNF217*	*ZNF703*

Select Rearrangements‡

ALK	*BCL2*	*BCR*	*BRAF*	*BRCA1*	*BRCA2*	*BRD4*	*EGFR*	*ETV1*
ETV4	*ETV5*	*ETV6*	*FGFR1*	*FGFR2*	*FGFR3*	*KIT*	*MSH2*	*MYB*
MYC	*NOTCH2*	*NTRK1*	*NTRK2*	*PDGFRA*	*RAF1*	*RARA*	*RET*	*ROS1*
TMPRSS2								

Tumor mutation burden

Advanced lung cancer (IIIB – IV)



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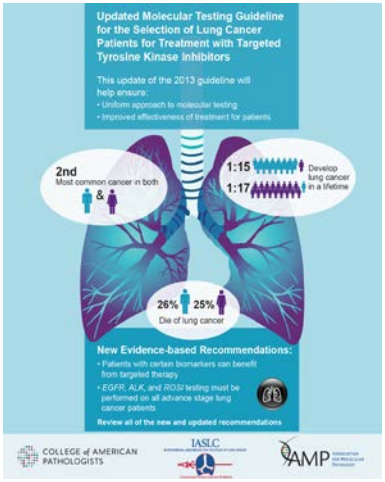
- "**Testing should extend** beyond those molecular alterations for which targeted therapies are approved by regulatory agencies…**to include molecular alterations for which there is compelling evidence of effective investigational targeted therapies** (and immunotherapies) **from published clinical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

Lindeman et al, JTO 2018;13:323

Advanced lung cancer (IIIB – IV)



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"Must-test" biomarkers as single-gene assay: standard of care for all patients	☛	**"Must-test" biomarkers: EGFR, ALK, ROS1, PD-L1 in all laboratories**
"Should-test" biomarkers: to direct patients to clinical trials (in larger gene panel)	☛	**"Should-test" biomarkers: expanded NGS panels (BRAF, MET, RET, HER2, KRAS)**
"Investigational" biomarkers: not yet applicable to clinical use	☛	**"Investigational" biomarkers: all the other genes**

Lindeman et al, JTO 2018;13:323

"Should-test" biomarkers

Table 4. Summary of 2017 Guideline Statements

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

Lindeman et al, JTO 2018;13:323

“Investigational” biomarkers

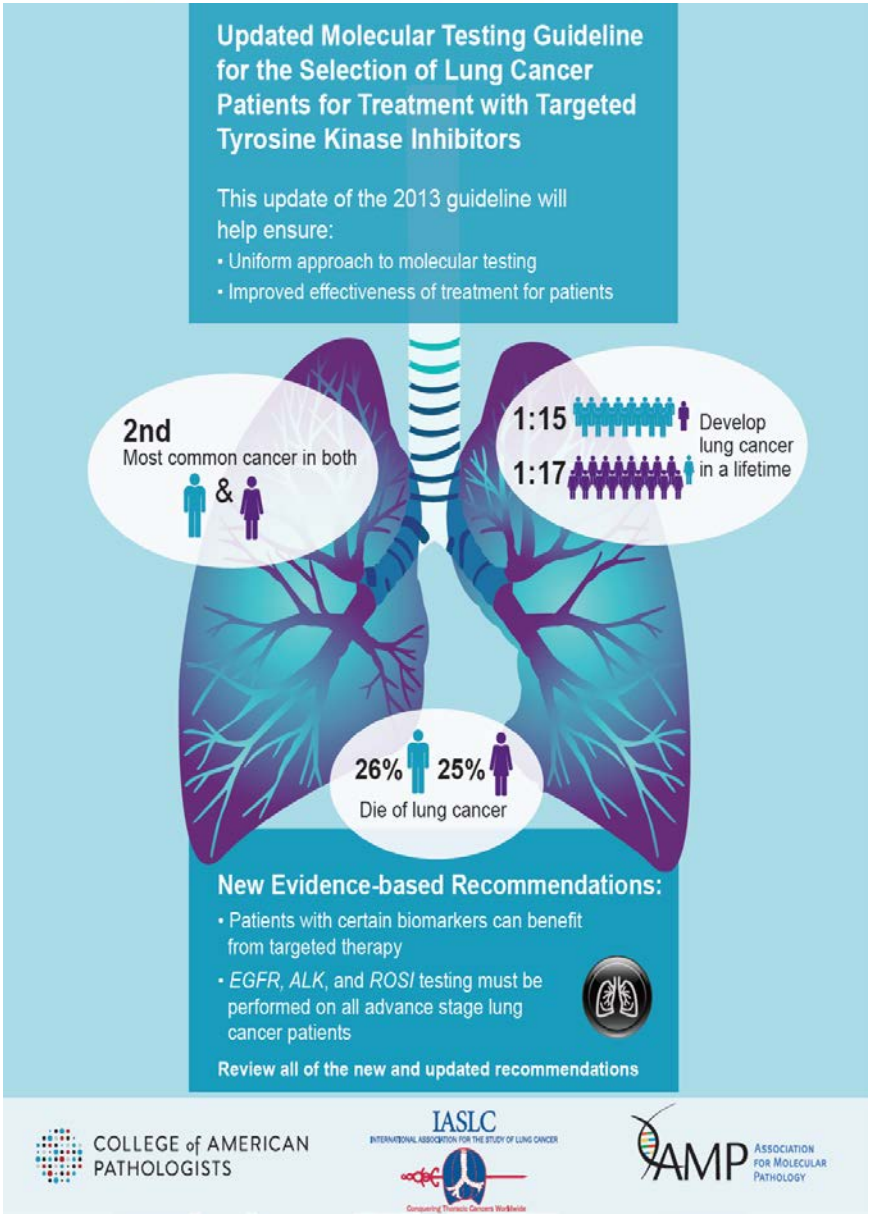
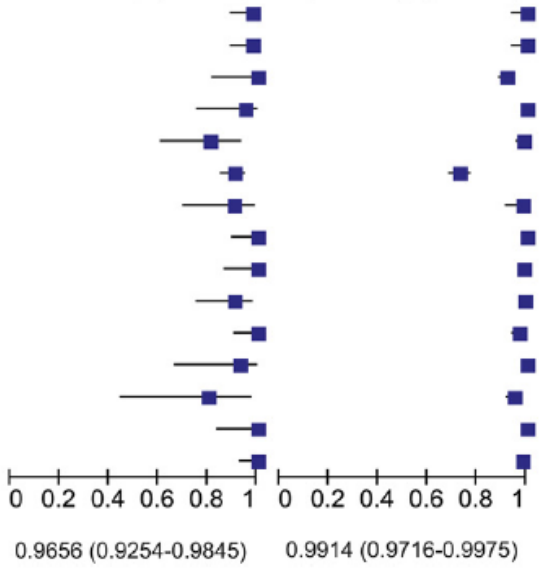


Table 5. Emerging Markers for Molecular Testing in Lung Cancer
Mitogen-activated protein kinase kinase 1 (*MEK1/MAP2K1*)
Fibroblast growth factor receptor 1-4 (*FGFR 1-4*)
Neurotrophic tyrosine kinase, receptor, type 1-3 (*NTRK1-3*)
Neuregulin 1 (*NRG1*)
Ras-like without CAAX 1 (*RIT1*)
Neurofibromin 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*)

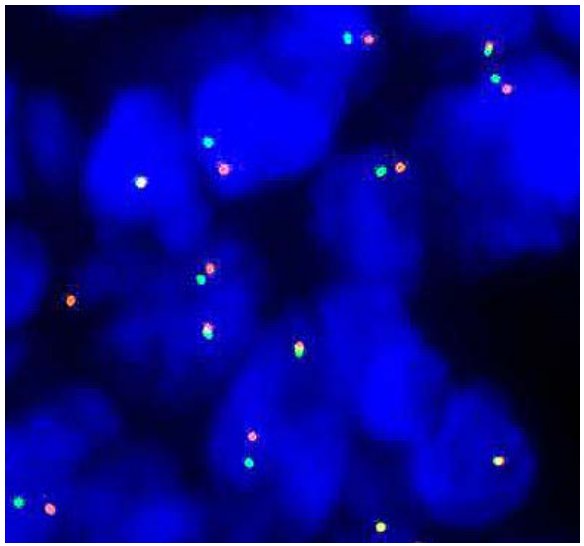
Lindeman et al, JTO 2018;13:323

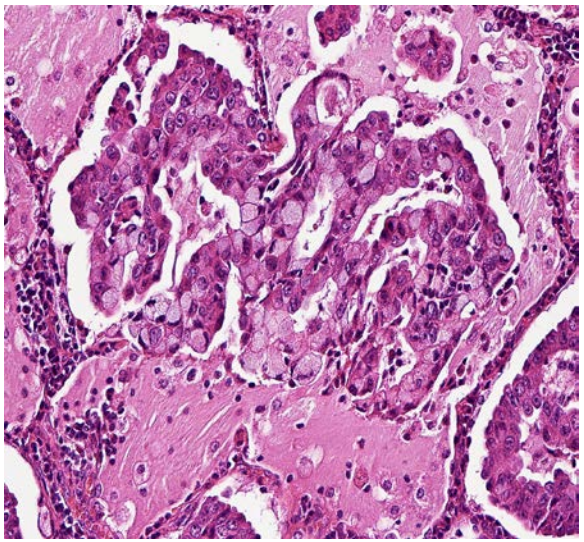
Advanced lung cancer: ALK by IHC

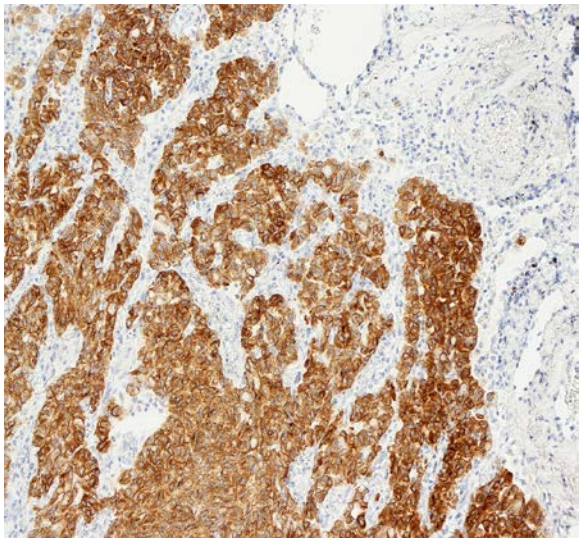
Study	TP	FP	FN	TN	Antibody	Cut-Off	Sensitivity (95% CI)	Specificity (95% CI)
Conde 2014[145]	46	0	1	56	5A4	2-3+	0.98 [0.89, 1.00]	1.00 [0.94, 1.00]
Conde 2014b[145]	46	0	1	56	D5F3	2-3+	0.98 [0.89, 1.00]	1.00 [0.94, 1.00]
Cutz 2014[146]	18	29	0	326	5A4	At least 1+	1.00 [0.81, 1.00]	0.92 [0.88, 0.94]
Gruber 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

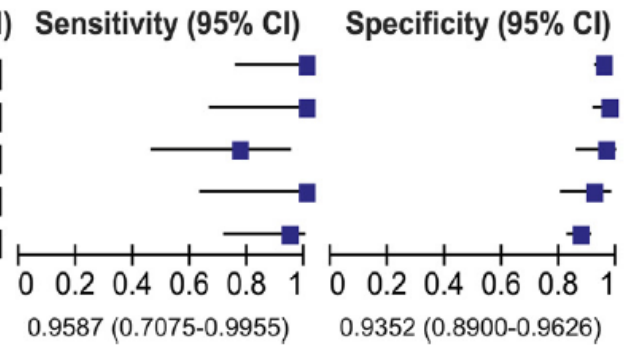




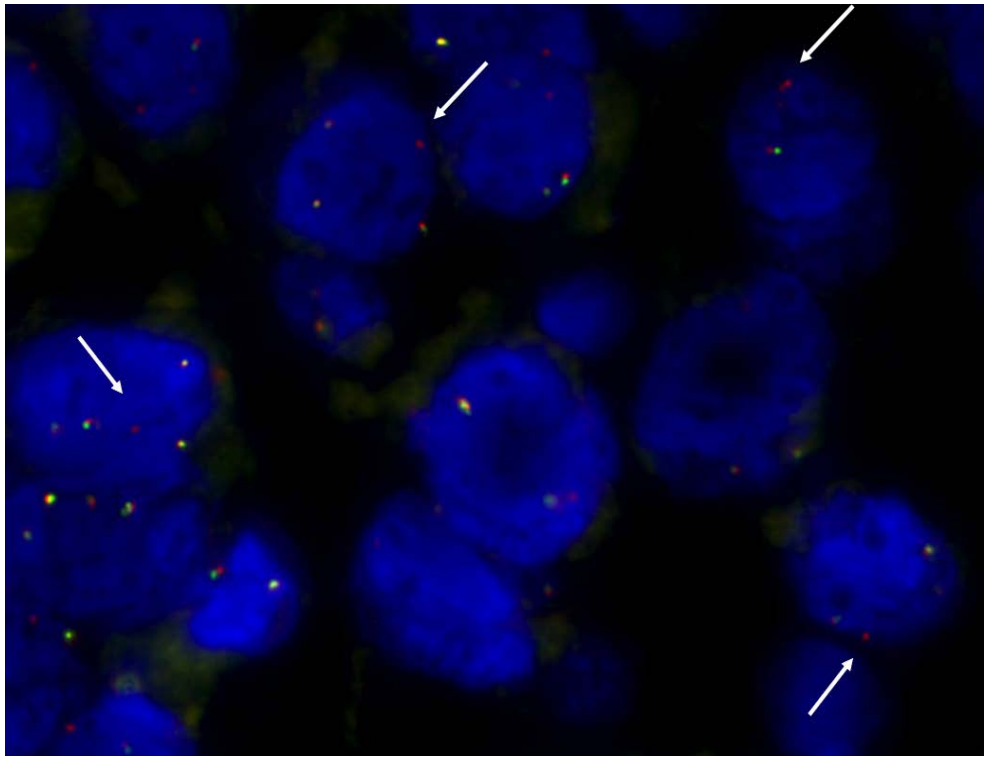


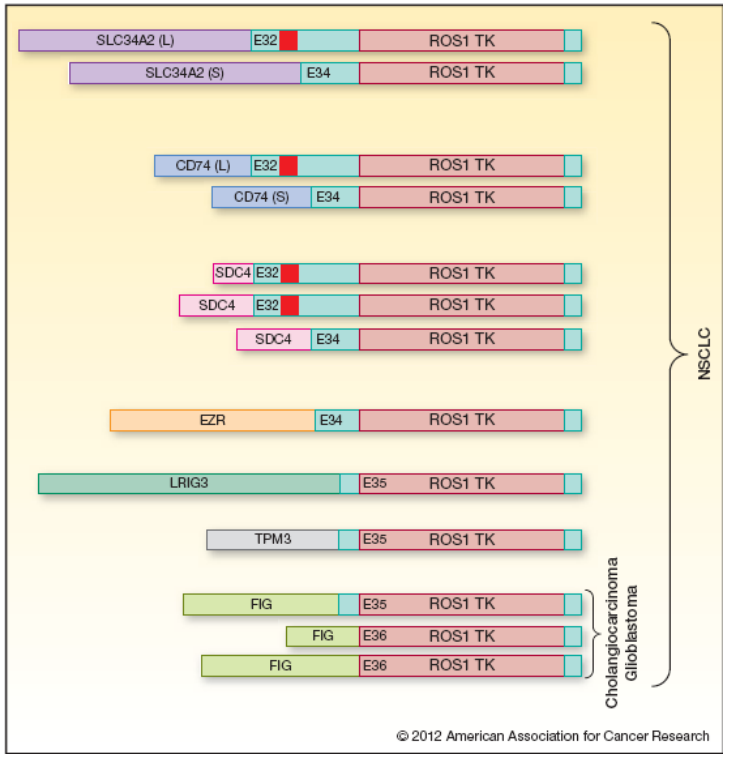
Advanced lung cancer: ROS-1 by FISH

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]



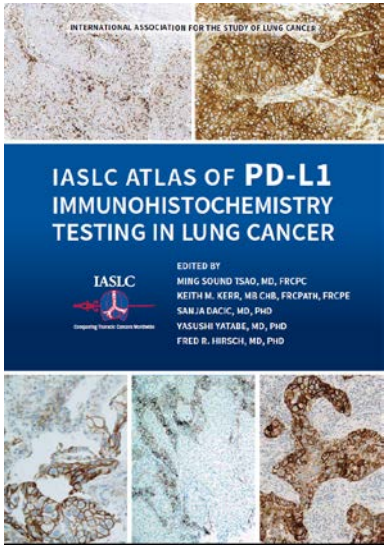
IHC 2+/3+ using mAb D4D6

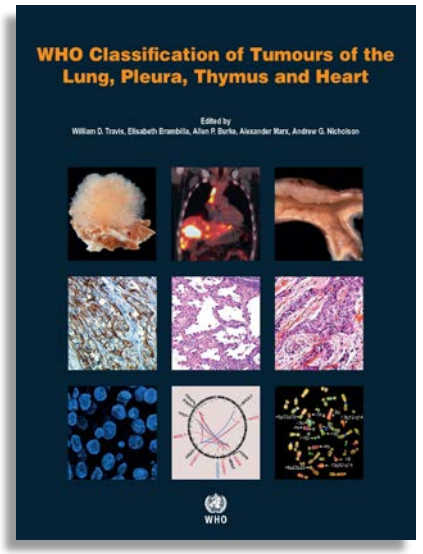




Molecular biology and lung cancer

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

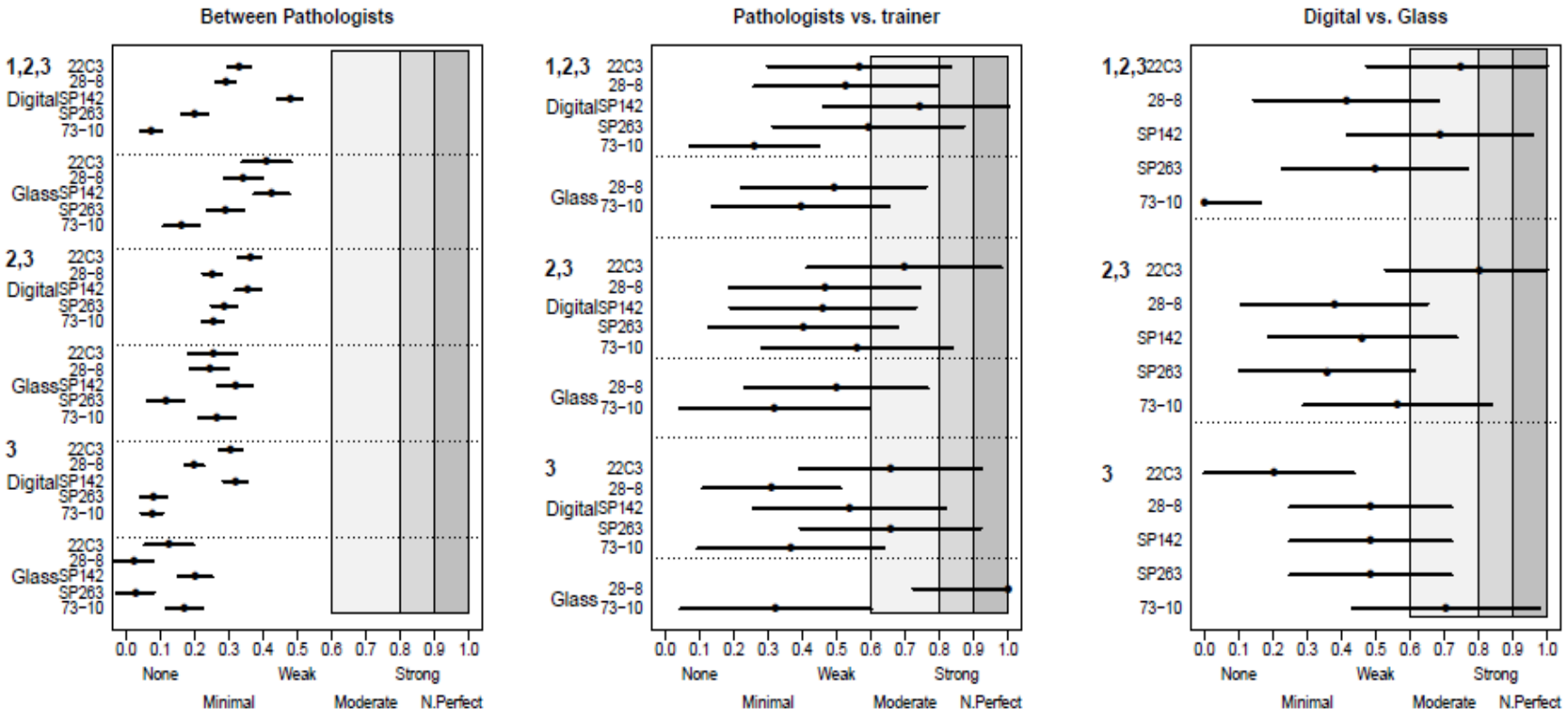




PD-L1 assay for immunotherapy

IASLC
INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER
IASLC 18TH WORLD CONFERENCE ON LUNG CANCER
October 15–18, 2017 | Yokohama, Japan
WWW.IASLC.ORG

Poor reliability for immune cell scoring



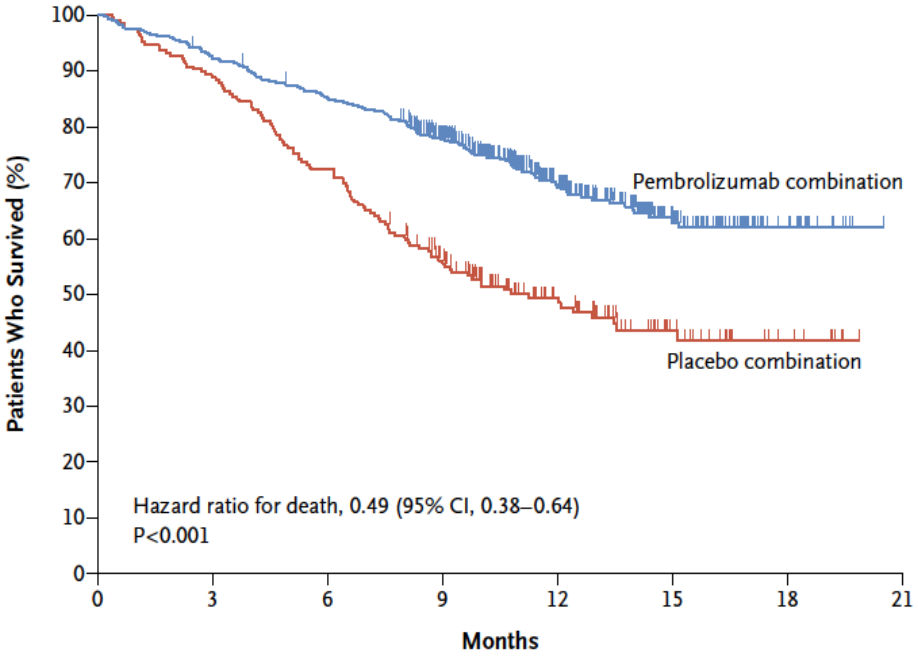
Fleiss Kappa Statistics **0.60-0.79: Moderate** **0.40-0.59: Weak** **0.21-0.39: Minimal**

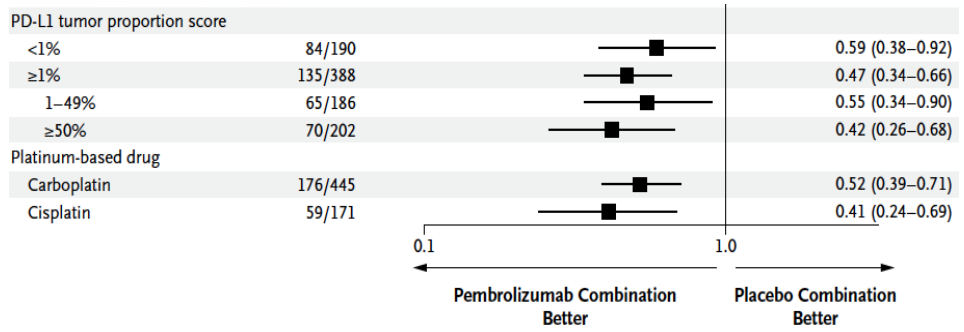
Tsao et al, JTO 2018

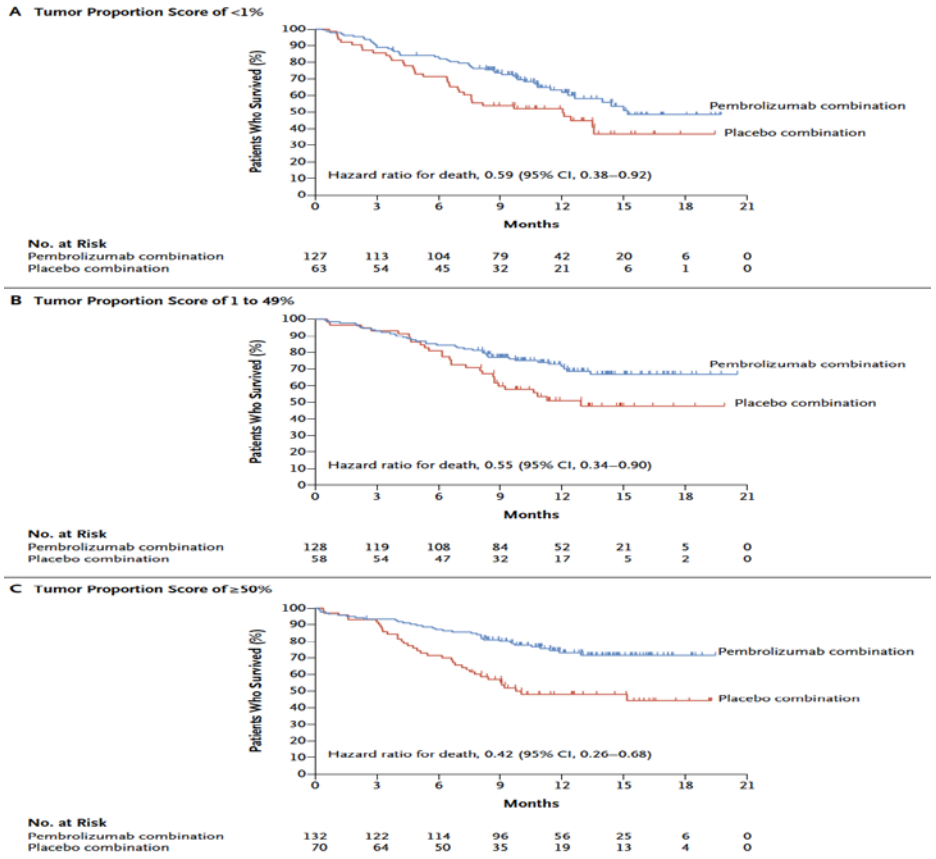
PD-L1 assessment for IT

Pembrolizumab plus Chemotherapy in Metastatic Non–Small-Cell Lung Cancer

L. Gandhi, D. Rodríguez-Abreu, S. Gadgeel, E. Esteban, E. Felip, F. De Angelis, M. Domine, P. Clingan, M.J. Hochmair, S.F. Powell, S.Y.-S. Cheng, H.G. Bischoff, N. Peled, F. Grossi, R.R. Jennens, M. Reck, R. Hui, E.B. Garon, M. Boyer, B. Rubio-Viqueira, S. Novello, T. Kurata, J.E. Gray, J. Vida, Z. Wei, J. Yang, H. Raftopoulos, M.C. Pietanza, and M.C. Garassino, for the KEYNOTE-189 Investigators*





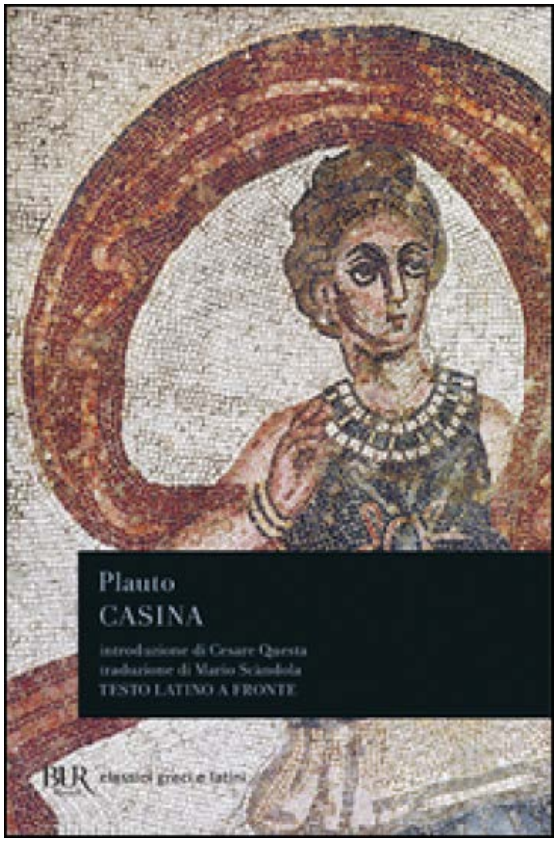


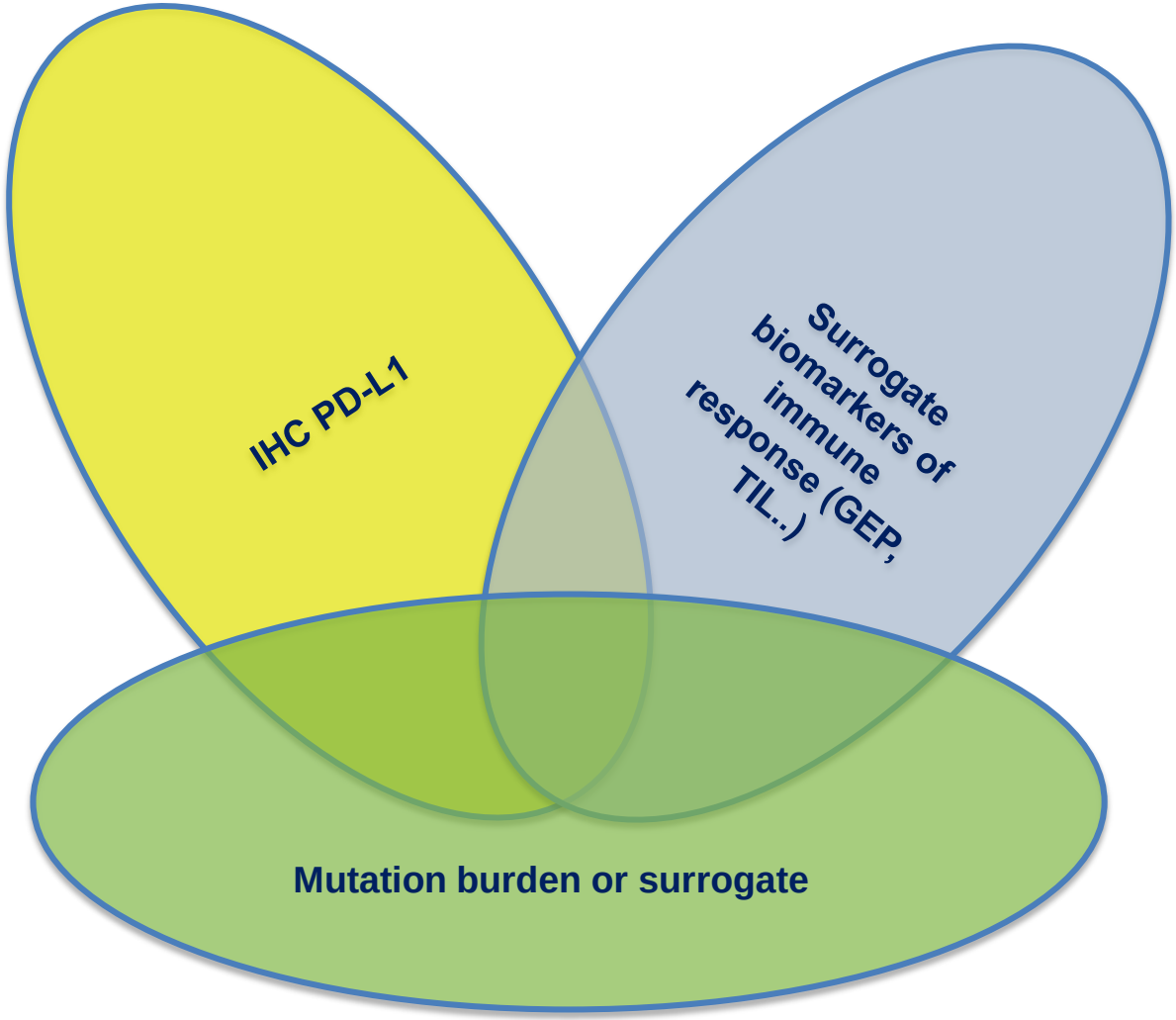
Pembro = pemetrexed + platin + pembro

Placebo = pemetrexed + platin + placebo

N Engl J Med 2018;378:2078-92.

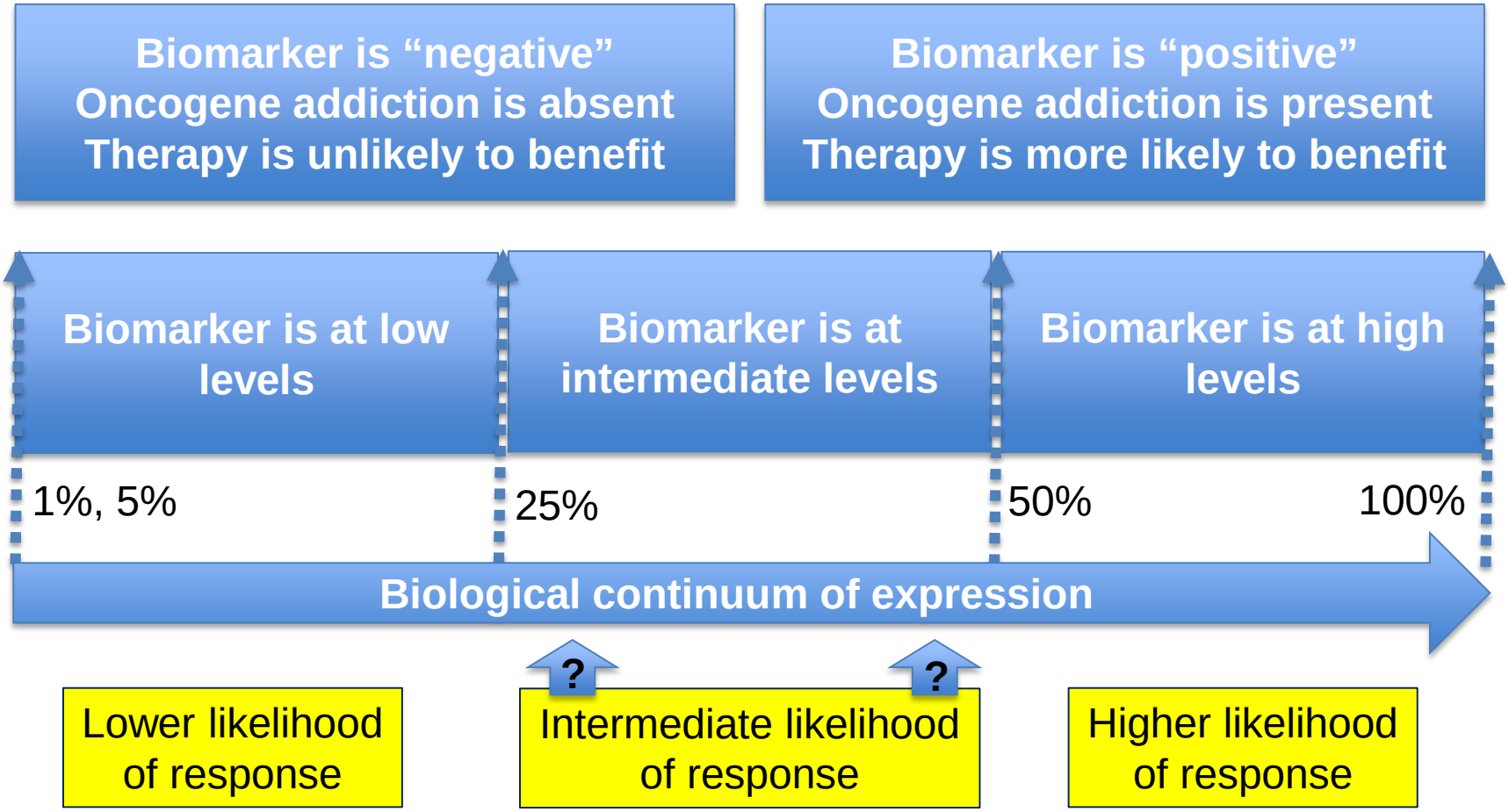
Quid ego nunc faciam?





Interpreting PD-L1 expression

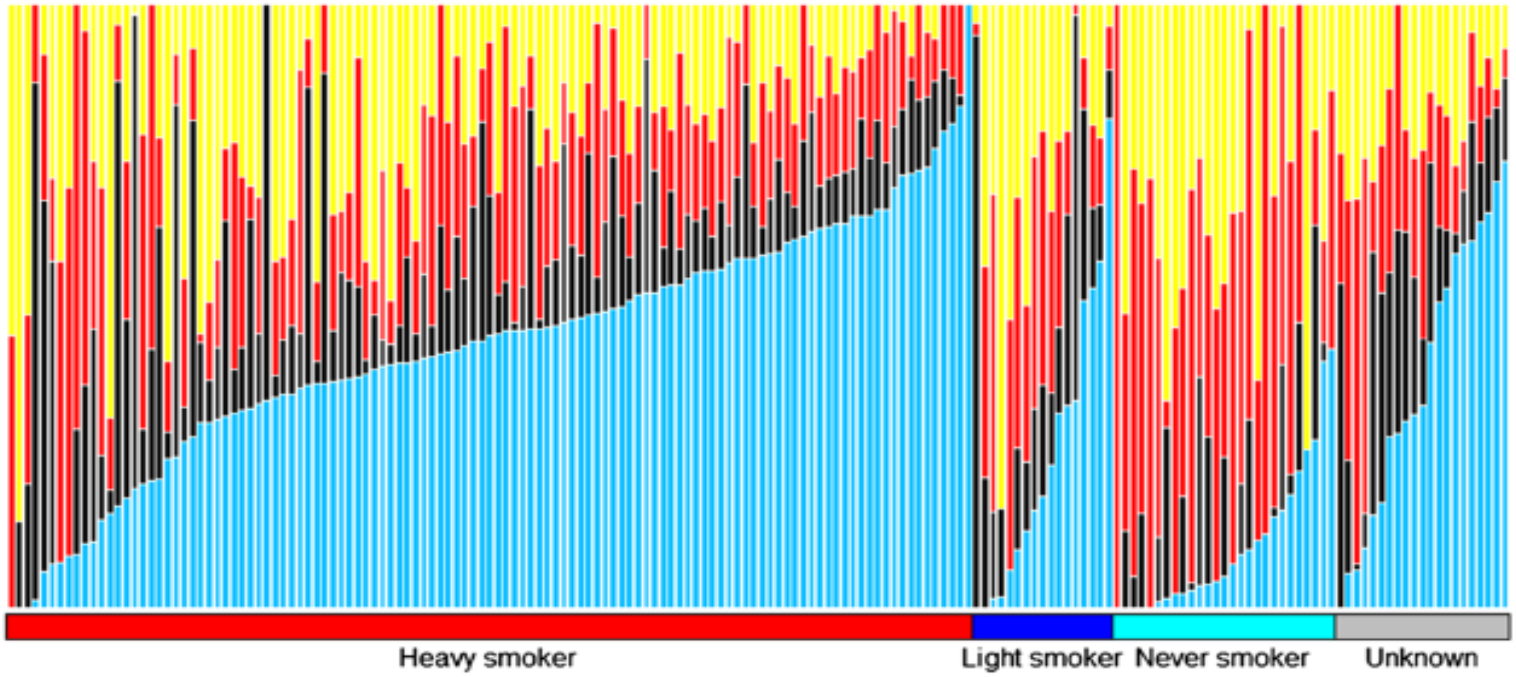
Differential effects depend upon a dose-response relationship



What is positive? Where should we set the cut-offs?

Tumor mutation burden for IT

Mutational smoking signature



Fingerprint mutation due to tobacco exposure is a C → A transversion, which is predominantly found in smokers

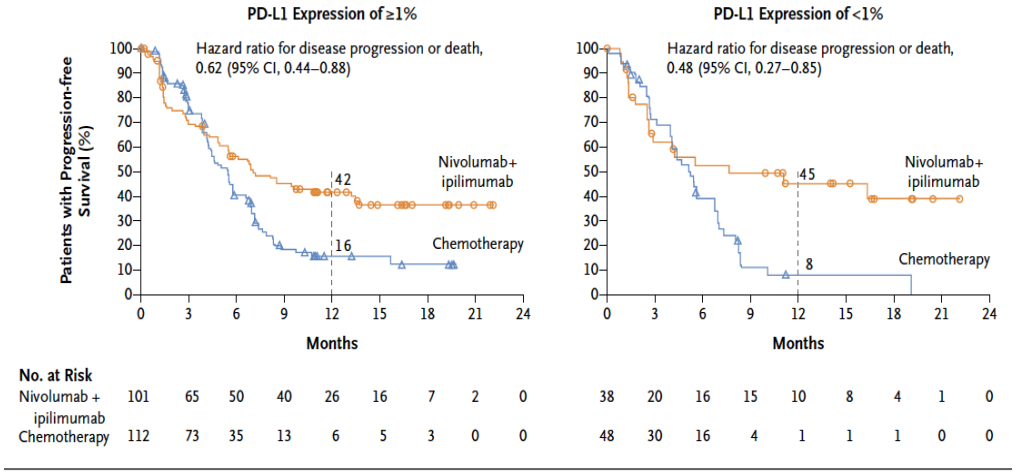
Jia *et al. BMC Medical Genomics* 2014

Tumor mutation burden for IT

Nivolumab plus Ipilimumab in Lung Cancer with a High Tumor Mutational Burden

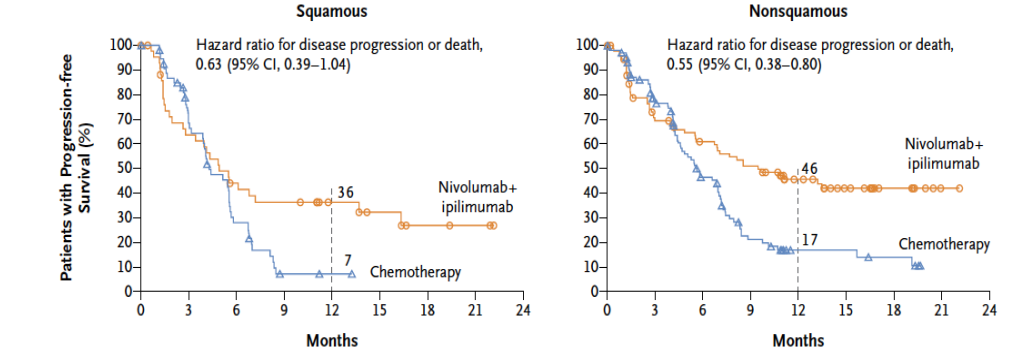
M.D. Hellmann, T.-E. Ciuleanu, A. Pluzanski, J.S. Lee, G.A. Otterson, C. Audigier-Valette, E. Minenza, H. Linardou, S. Burgers, P. Salman, H. Borghaei, S.S. Ramalingam, J. Brahmer, M. Reck, K.J. O'Byrne, W.J. Geese, G. Green, H. Chang, J. Szustakowski, P. Bhagavatheeswaran, D. Healey, Y. Fu, F. Nathan, and L. Paz-Ares

A Tumor PD-L1 Expression



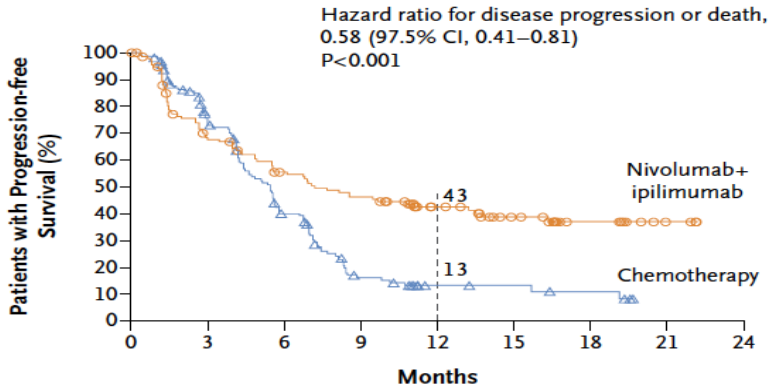
No. at Risk									
Nivolumab + ipilimumab	101	65	50	40	26	16	7	2	0
Chemotherapy	112	73	35	13	6	5	3	0	0
Nivolumab + ipilimumab	38	20	16	15	10	8	4	1	0
Chemotherapy	48	30	16	4	1	1	1	0	0

B Tumor Histologic Type



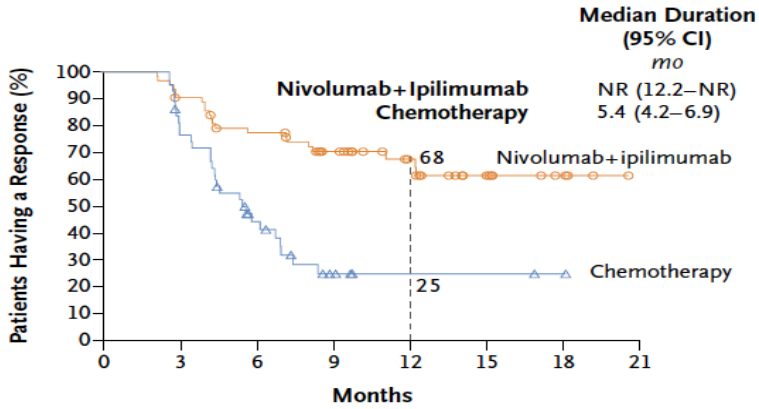
at least 10 mutations per megabase

A Progression-free Survival



No. at Risk									
Nivolumab + ipilimumab	139	85	66	55	36	24	11	3	0
Chemotherapy	160	103	51	17	7	6	4	0	0

B Duration of Response



No. at Risk								
Nivolumab + ipilimumab	63	56	46	32	22	10	5	0
Chemotherapy	43	32	15	5	2	2	1	0

Survival by TMB

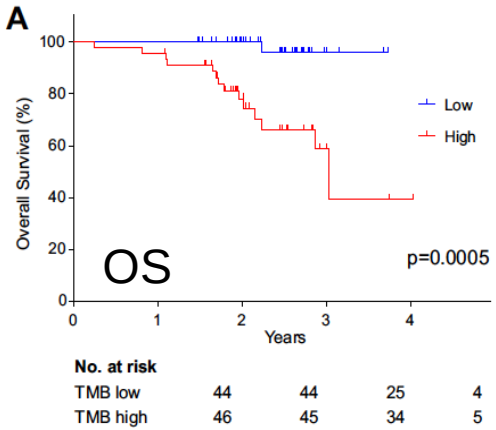
Prognostic Impact of Tumor Mutation Burden in Patients With Completely Resected Non-Small Cell Lung Cancer: Brief Report

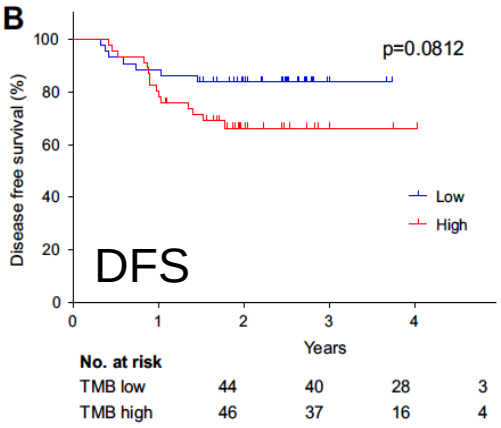
Yuki Owada-Ozaki, MD,[a] Satoshi Muto, MD, PhD,[a] Hironori Takagi, MD,[a] Takuya Inoue, MD,[a] Yuzuru Watanabe, MD,[a] Mitsuro Fukuhara, MD,[a] Takumi Yamaura, MD, PhD,[a] Naoyuki Okabe, MD, PhD,[a] Yuki Matsumura, MD,[a] Takeo Hasegawa, MD, PhD,[a] Jun Ohsugi, MD, PhD,[a] Mika Hoshino, MD, PhD,[a] Yutaka Shio, MD, PhD,[a] Hideaki Nanamiya, PhD,[b] Jun-ichi Imai, PhD,[b] Takao Isogai, PhD,[b] Shinya Watanabe, MD, PhD,[b] Hiroyuki Suzuki, MD, PhD[a,*]

IASLC

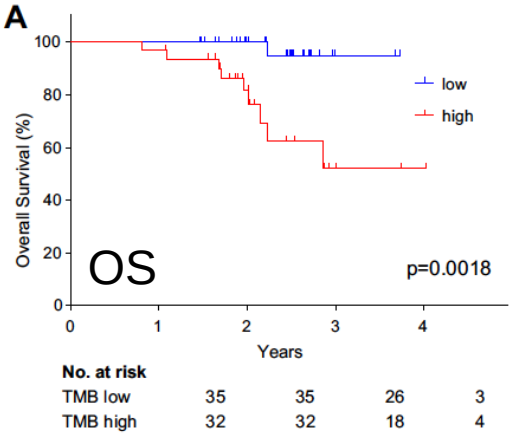
Journal of Thoracic Oncology

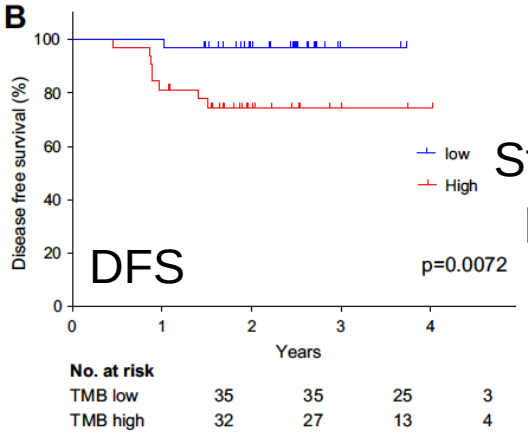
Available online - 11 April 2018





All pats





Stage I pats

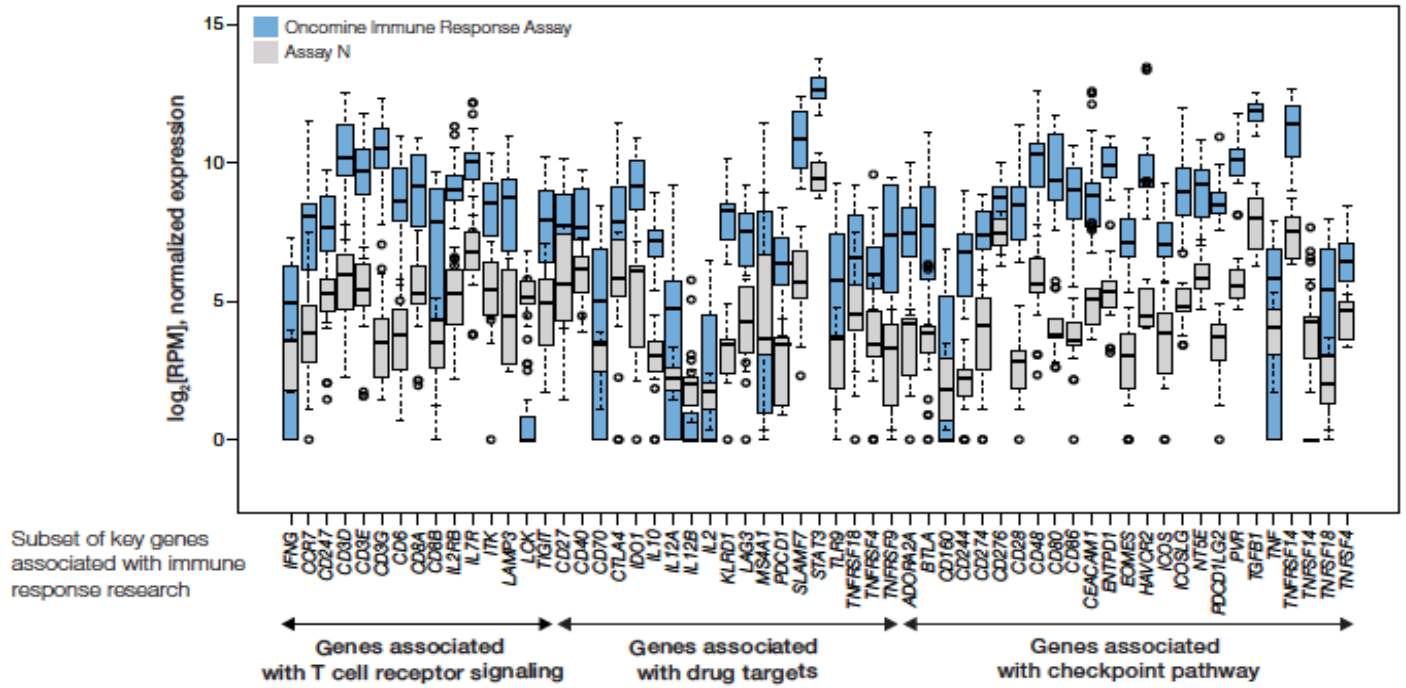
WES: any mutation, cut-off 62

	N = 90	
Median age, yrs (range)	70 (40-87)	
Gender		
Male / female	63 (70.0%) / 27 (30.0%)	
Smoking status		
Never smoker	28	(31.1%)
Former or current smoker	62	(68.9%)
Median brinkman Index (range)	675 (45-2580)	
Tumor size, cm (range)	2.8 (0.8-11.0)	
Histology		
Adenocarcinoma	63	(70.0%)
Squamous cell carcinoma	27	(30.0%)
EGFR-mutation		
Exon21;L858R	14	(15.5%)
Exon19 deletion	8	(8.9%)
Others	2	(2.2%)
Wild-type/Unknown	66	(73.3%)
Pathological stage		
IA	43	(47.8%)
IB	24	(26.7%)
IIA	4	(4.4%)
IIB	8	(8.9%)
IIIA	9	(10.0%)
IIIB	2	(2.2%)
Adjuvant therapy		
Platinum	8	
Others	15	
Recurrence	22	(24.4%)
Treatment for recurrence		
Platinum	10	
EGFR-TKI	5	
Others	5	
Best supportive care	2	
Death	15	(16.7%)
Median TMB (range)	62	(10-502)

Immune checkpoint by…

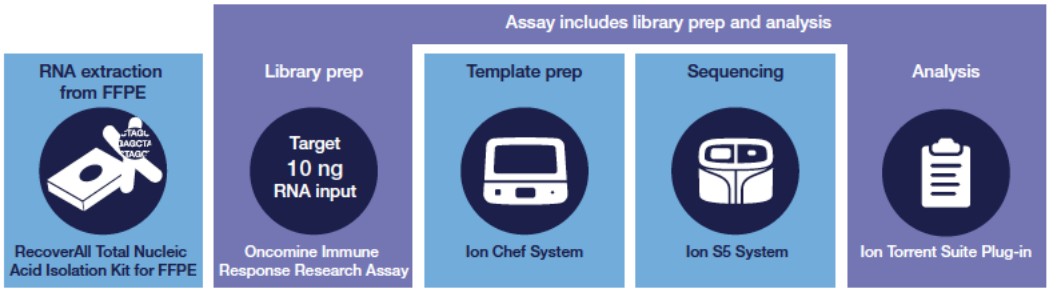
ThermoFisher SCIENTIFIC

Oncomine Immune Response Research Assay



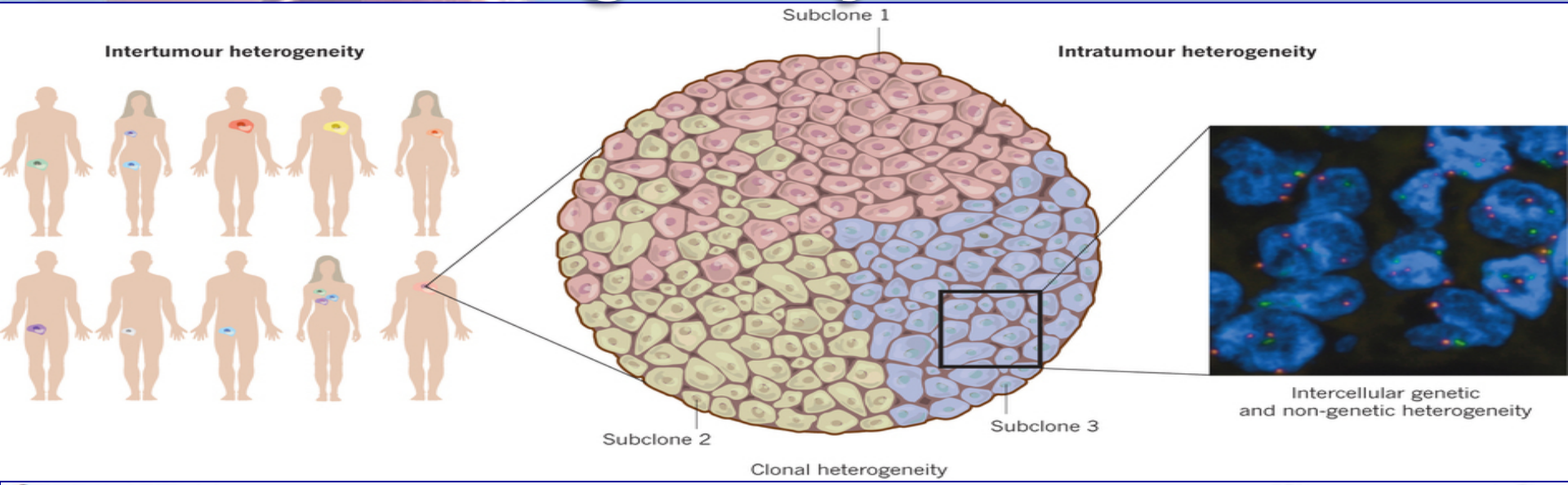
- 395 genes
- 36 functional annotation groups

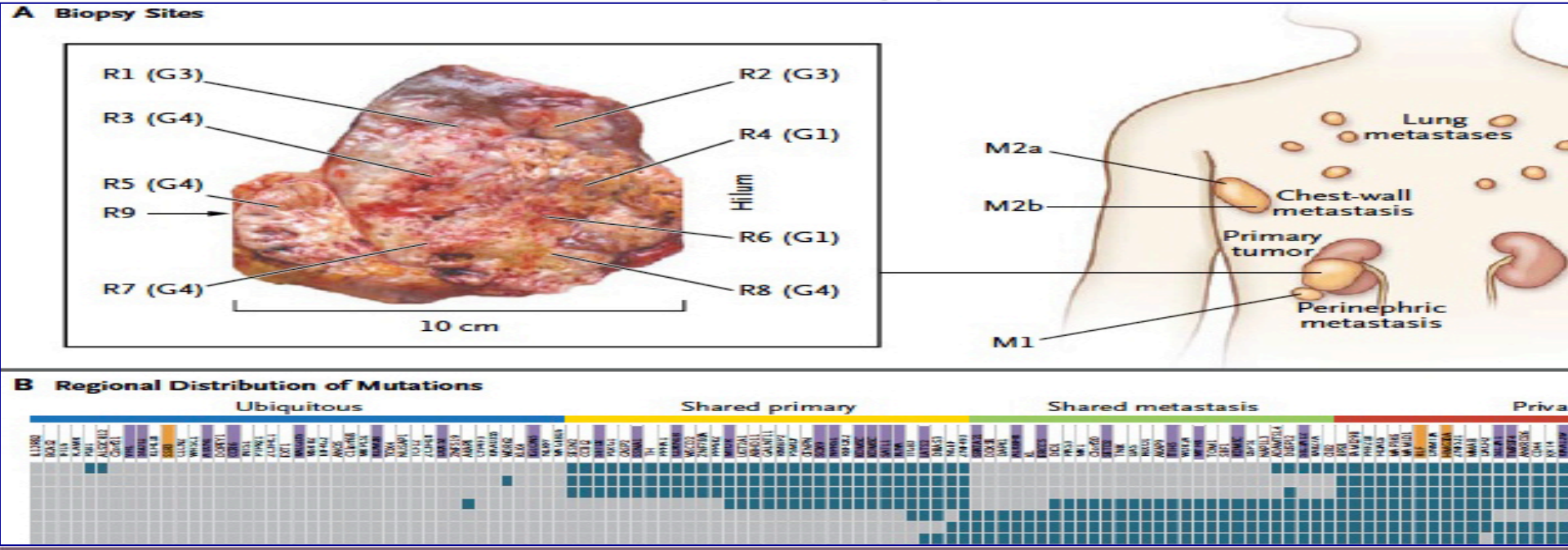
Functional annotation group	No. of genes
Adhesion, migration	14
Antigen presentation	3
Antigen processing	19
Apoptosis	4
B cell marker	11
B cell receptor signaling	3
Checkpoint pathway	30
Chemokine signaling	10
Cytokine signaling	15
Dendritic cell	7
Dendritic cell, macrophage	6
Drug target	21
Helper T cells	8
Housekeeping	11
Innate immune response	11
Interferon signaling	8
Leukocyte inhibition	2
Leukocyte migration	5
Lymphocyte activation	2
Lymphocyte development	3
Lymphocyte infiltrate	46
Macrophage	5
Myeloid marker	7
Neutrophil	5
NK activation	8
NK cell marker	4
PD-1 signaling	9
Proliferation	10
T cell differentiation	2



Functional annotation group	No. of genes
T cell receptor signaling	6
T cell regulation	9
TCR coexpression	19
Tumor antigen	17
Tumor marker	27
Type I interferon signaling	8
Type II interferon signaling	23

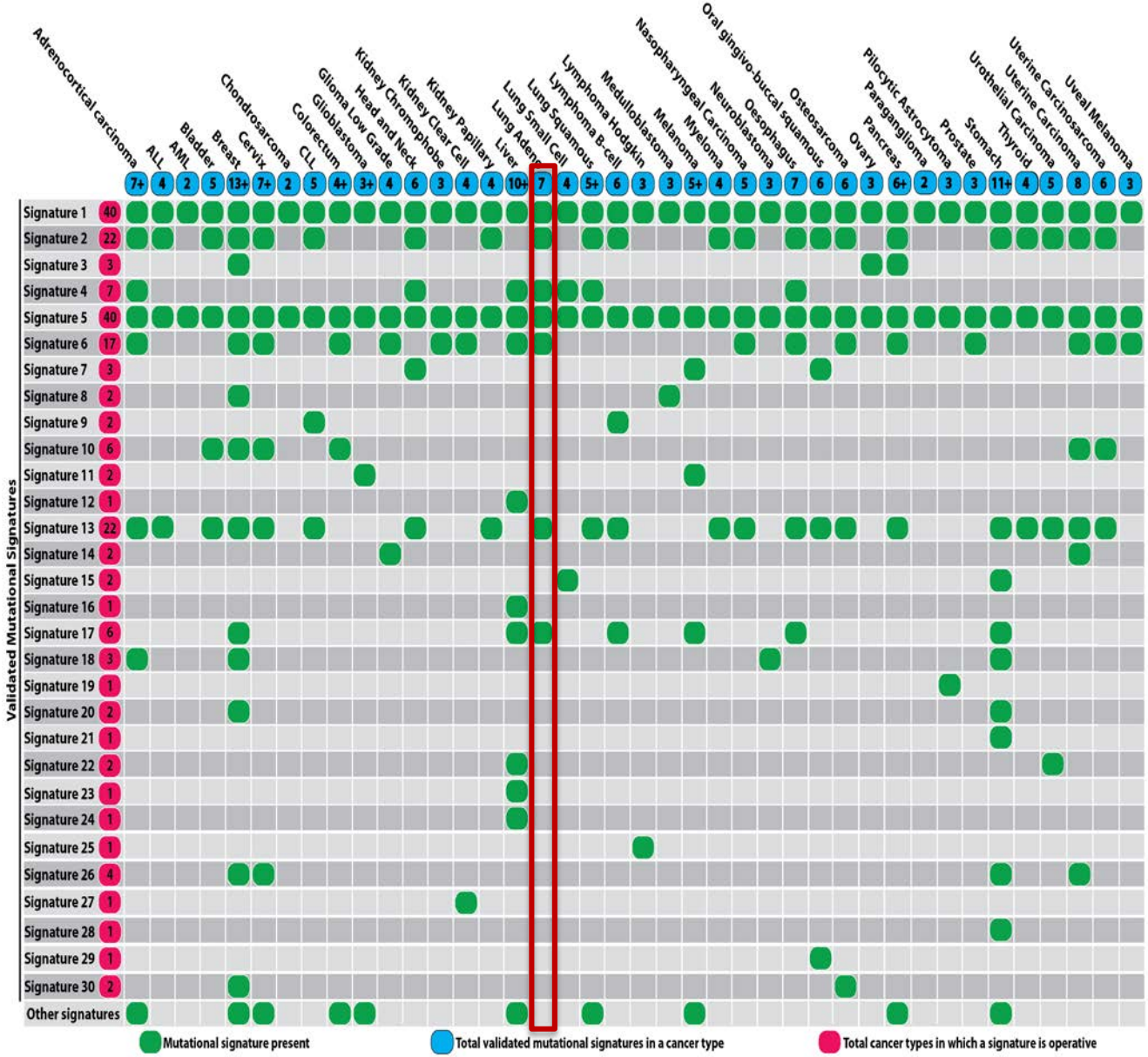
Tumor heterogeneity



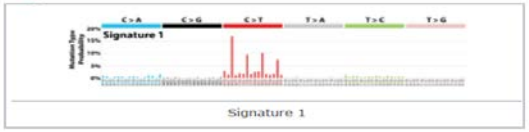


Tumor heterogeneity

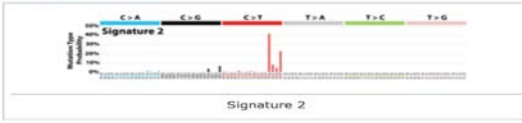
COSMIC
Catalogue of somatic mutations in cancer



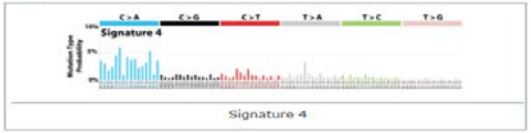
Signature 1 spontaneous deamination



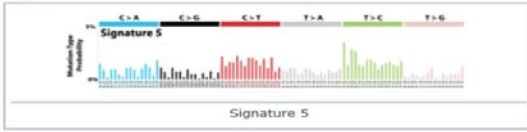
Signature 2 APOBEC activity



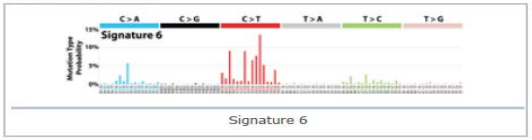
Signature 4 smoke-related DNA damage



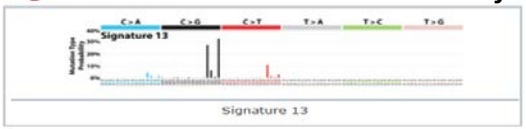
Signature 5 unknown



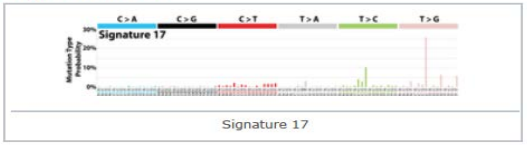
Signature 6 microsatellite instability



Signature 13 APOBEC activity



Signature 17 unknown



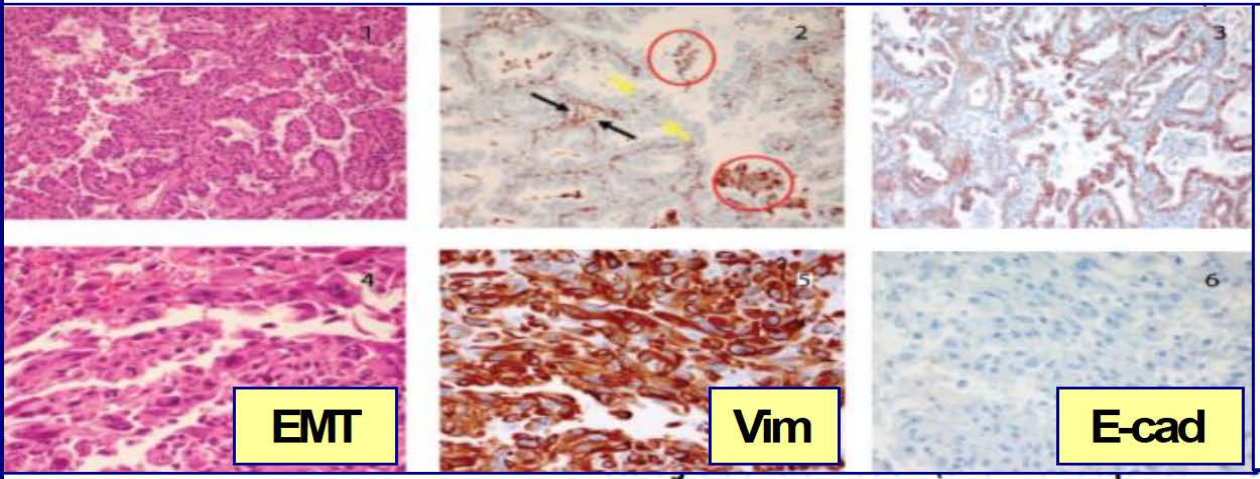
Tumor heterogeneity

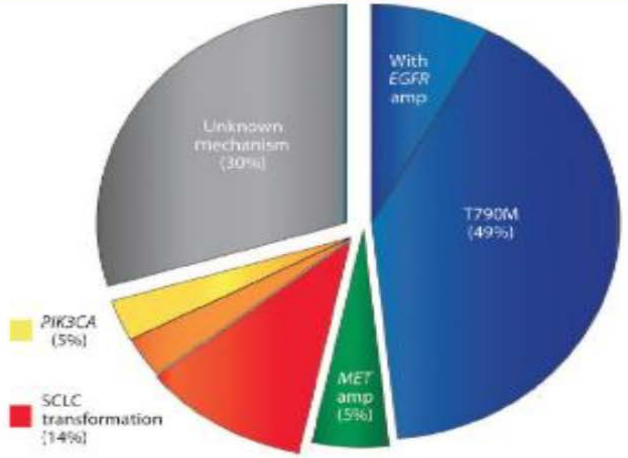
Science Translational Medicine
AAAS

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

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 fi skipping the current pathogenesis paradigm

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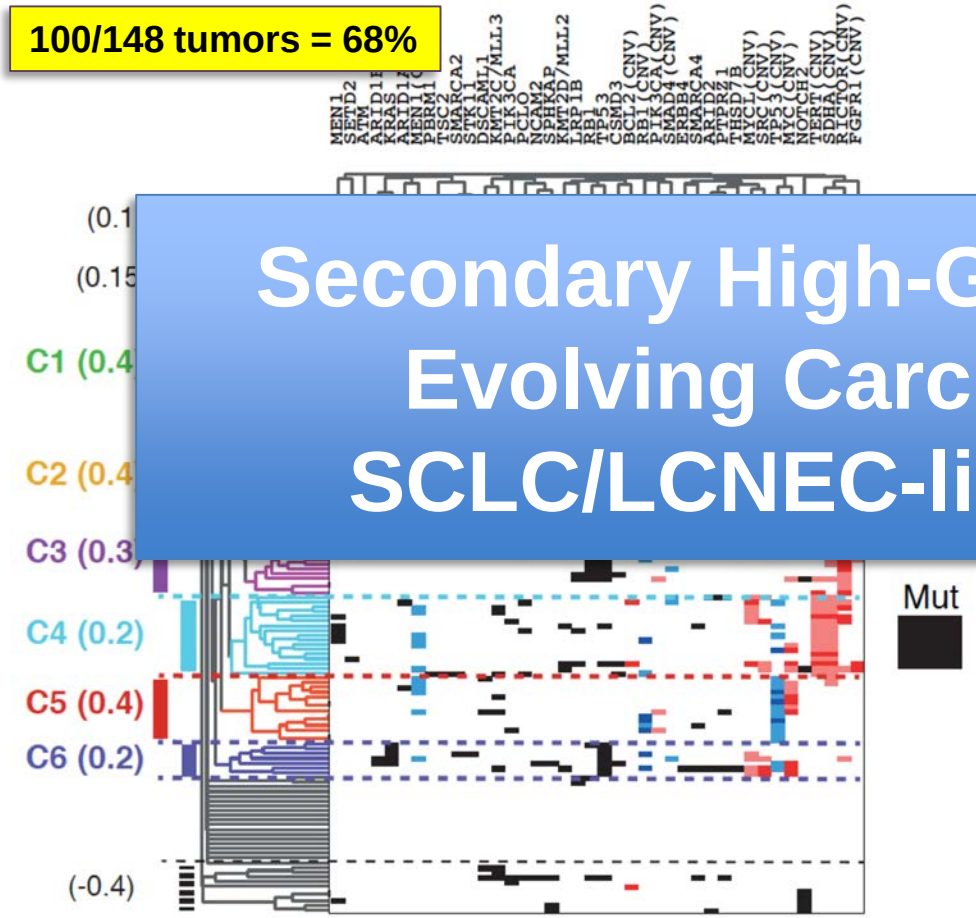
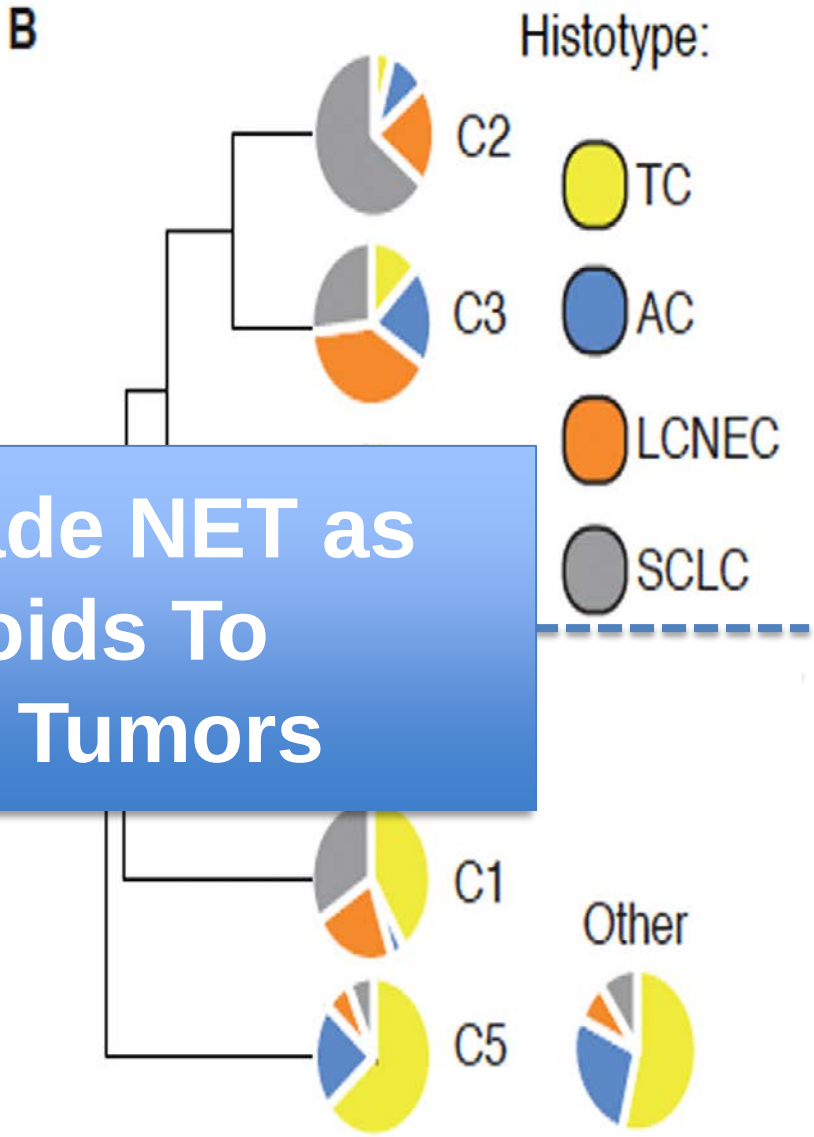
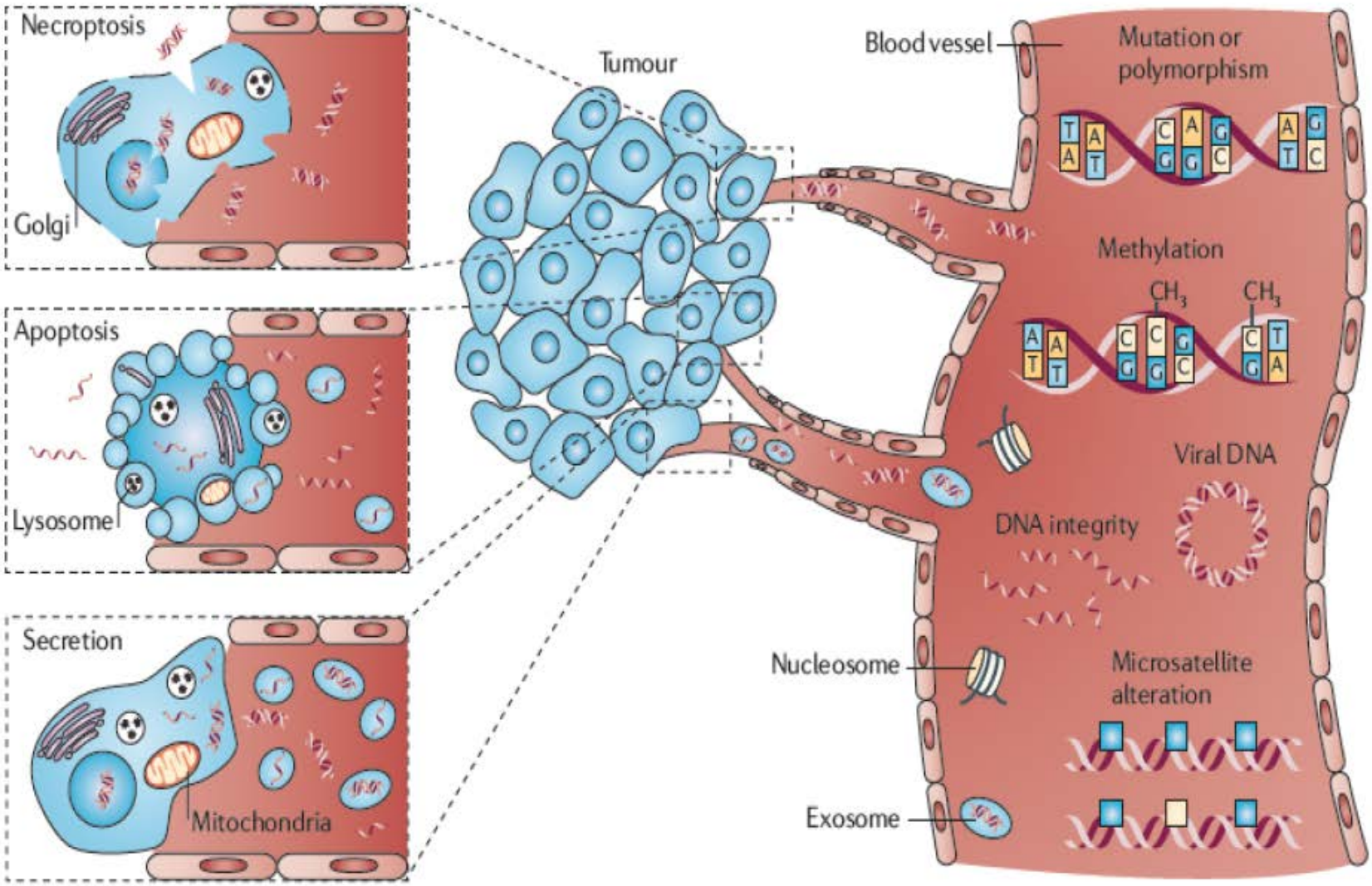
100/148 tumors = 68%





Secondary High-Grade NET as Evolving Carcinoids To SCLC/LCNEC-like Tumors

Liquid biopsy over time

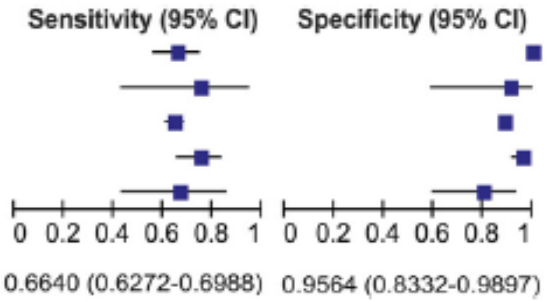


Schwarzenbach et al., Nat Rev Cancer 2011

cfDNA testing in liquid biopsy

- **Rec:** 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%

- **Exp. Cons. Op.:** It is possible to identify T790M in ADC patients with progression or secondary clinical resistance to EGFR-TKI; **testing of tumor samples is recommended if the plasma result is negative**

- **No Rec:** 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

Rec: recommendation; ECO: expert consensus opinion

Lindeman, JTO 2018


thank you
danke
рахмат
謝謝
ngiyabonga
teşekkür ederim
Баярлалаа
спасибо
faafetai lava
mersi
kia ora
barka
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dank je
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