Molecular Diagnosis of Lung Cancer

In-Jae Oh

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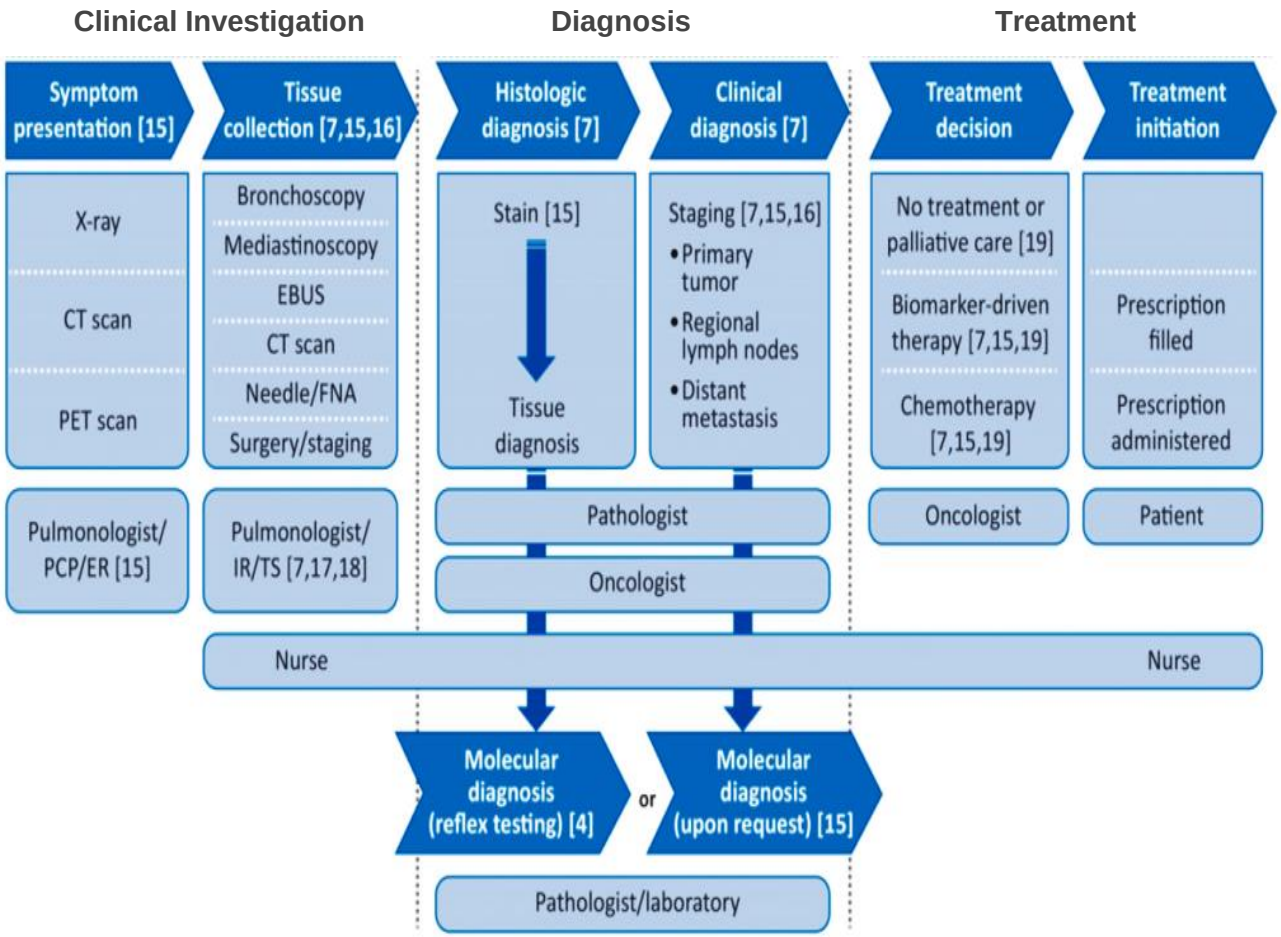
Division of Lung Cancer Clinic,

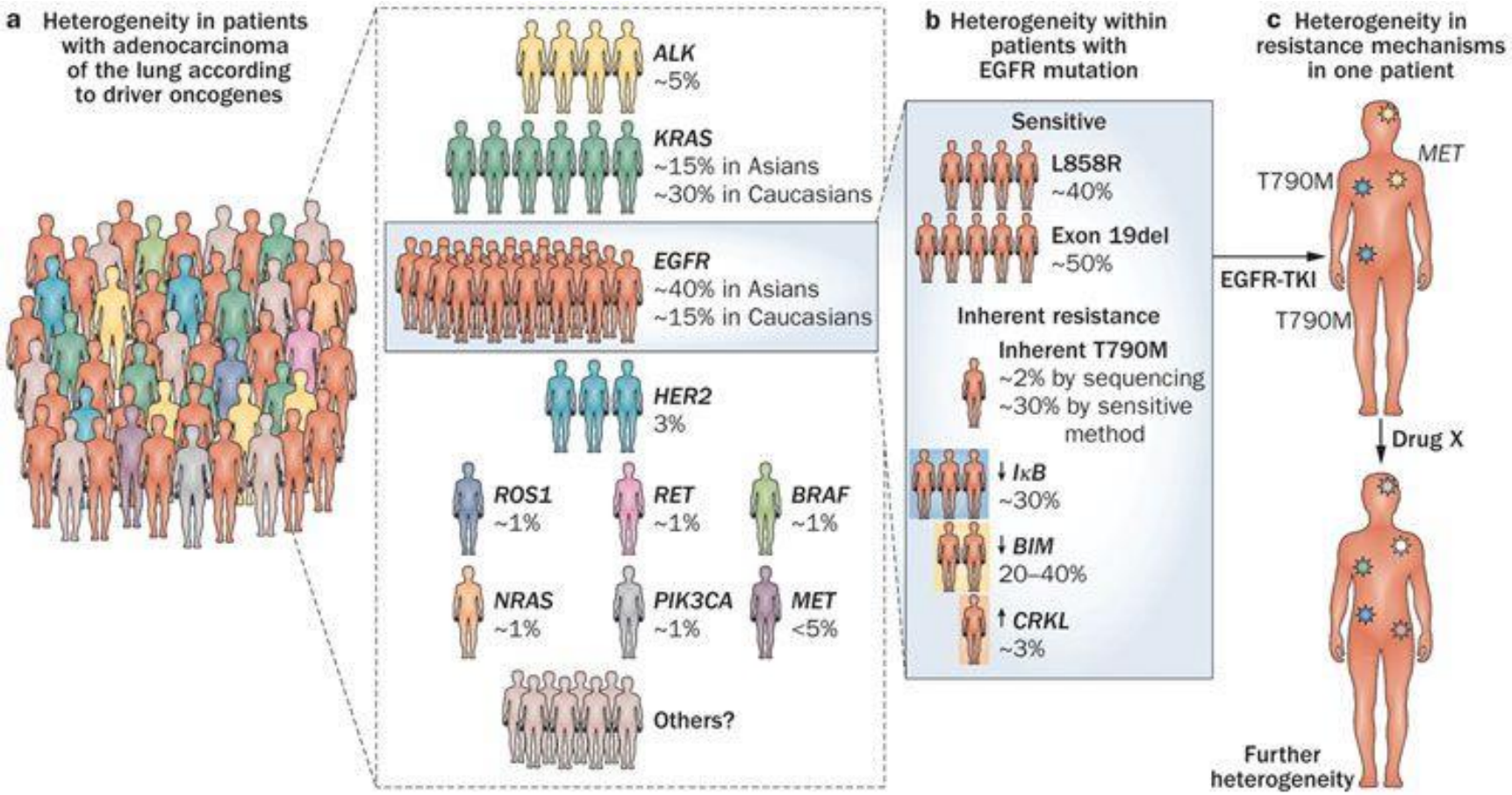
Chonnam National University Hwasun Hospital

The Journey of Lung Cancer Patients



Source: Levy BP et al. The Oncologist 2015Oct:20(10)1175-81

Various classes of tumor heterogeneity in adenocarcinoma of the lung



Mitsudomi, T. *et al*. (2013) Surgery for NSCLC in the era of personalized medicine
Nat. Rev. Clin. Oncol. doi:10.1038/nrclinonc.2013.22

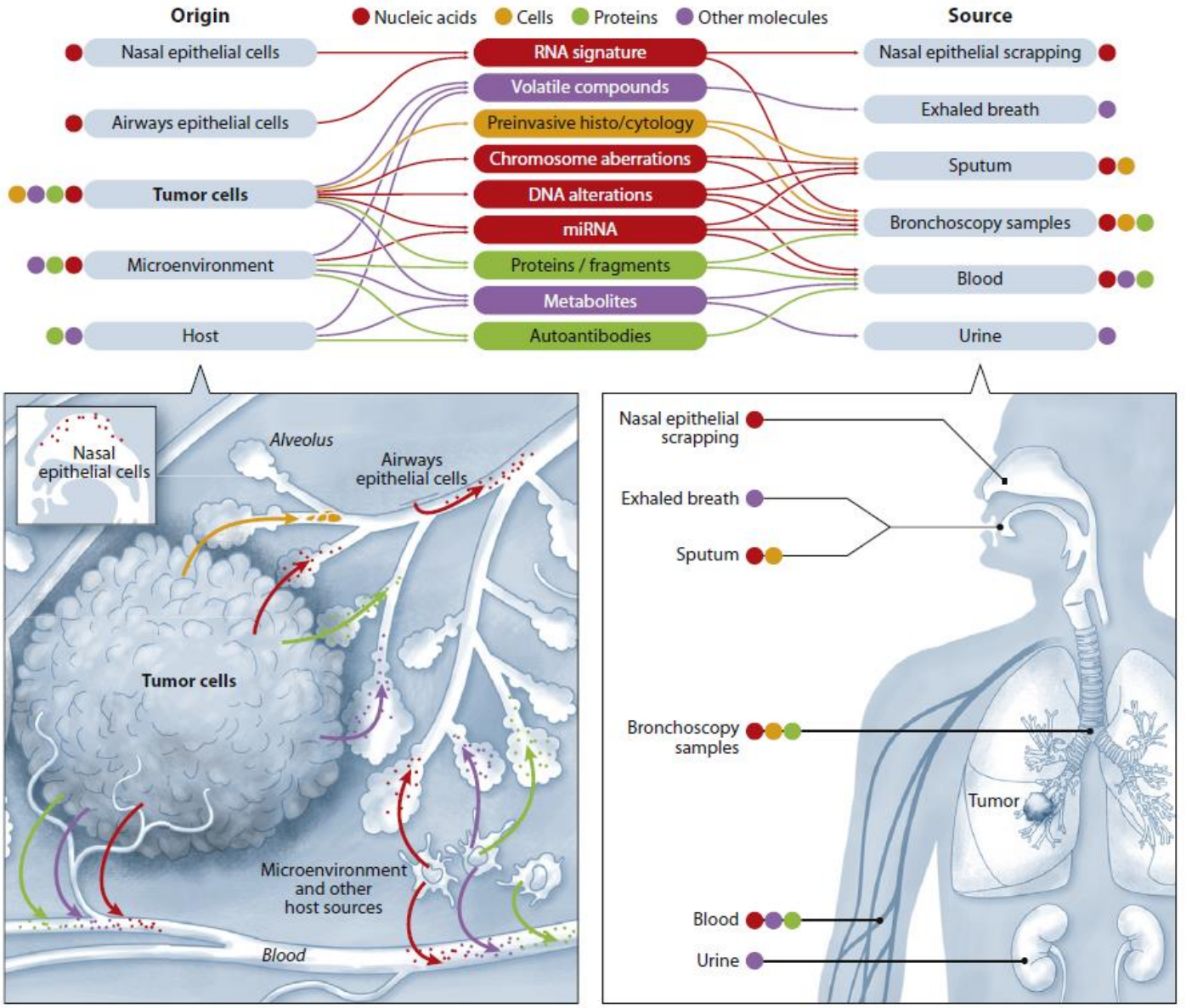


Figure 2. Currently explored biomarker candidates. miRNA, microRNA.

J Thorac Oncol 2019;14(3):343-357

Biomarker development in the precision medicine era

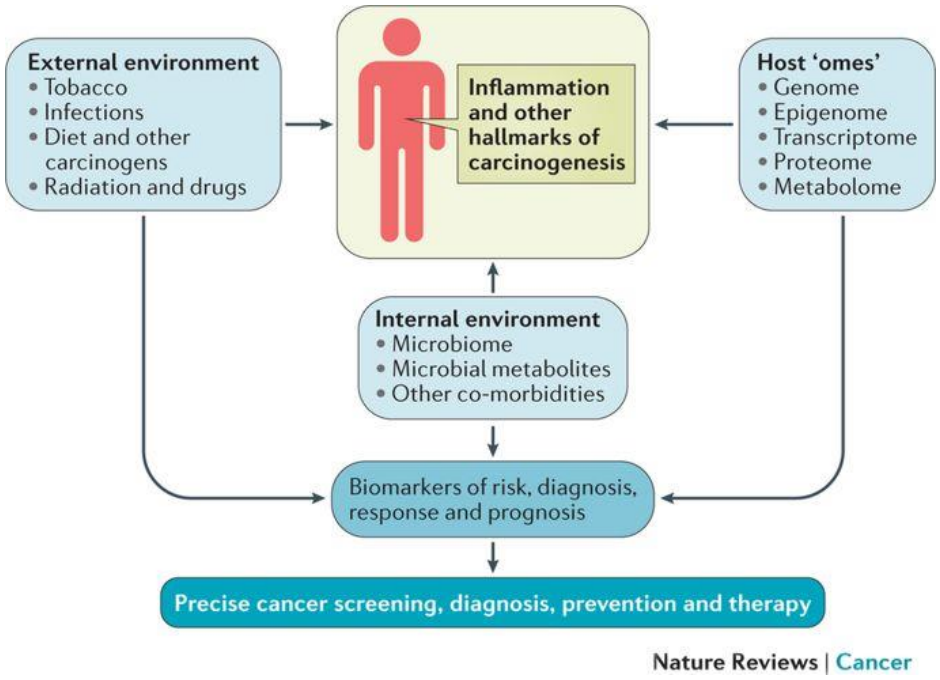


Figure 4. The lung exposome

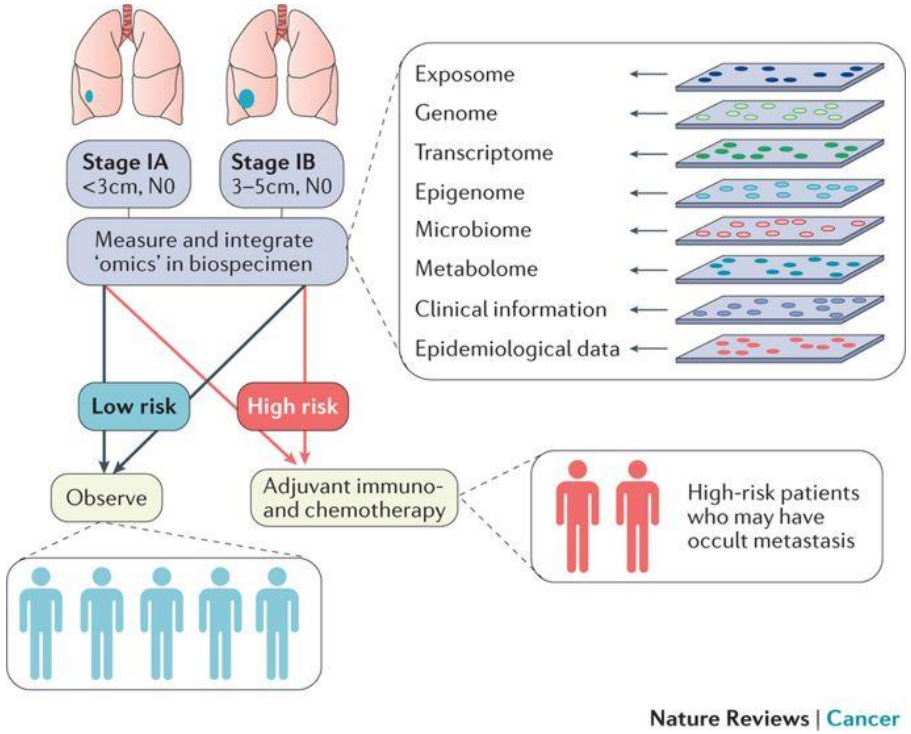


Figure 5. Use of precision medicine to classify patients with early-stage lung cancer into subclasses to provide appropriate treatment

Nature Reviews Cancer 2016;16:525–537

Liquid biopsies come of age
: challenges to implementing ctDNA-based screening and MRD detection

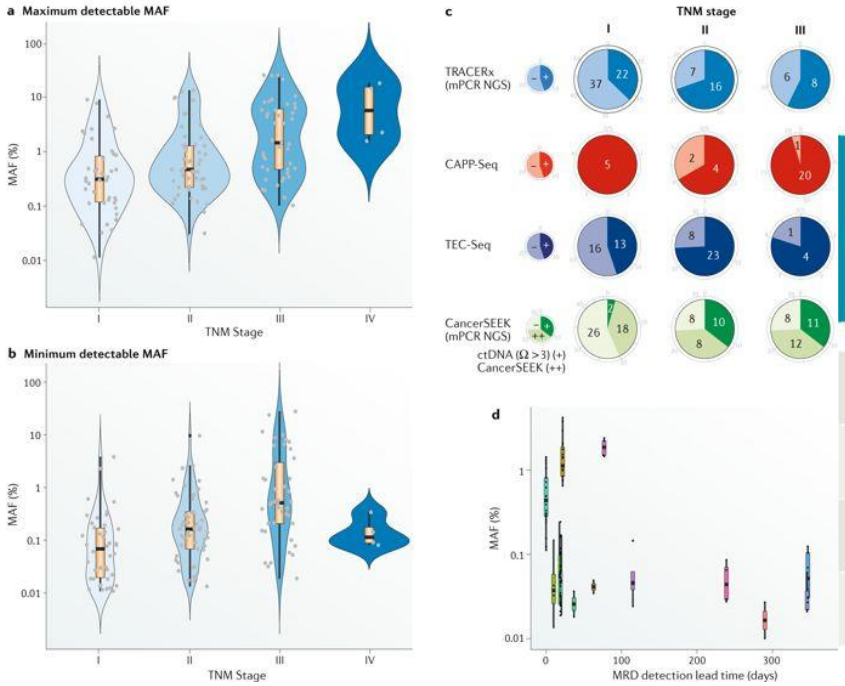
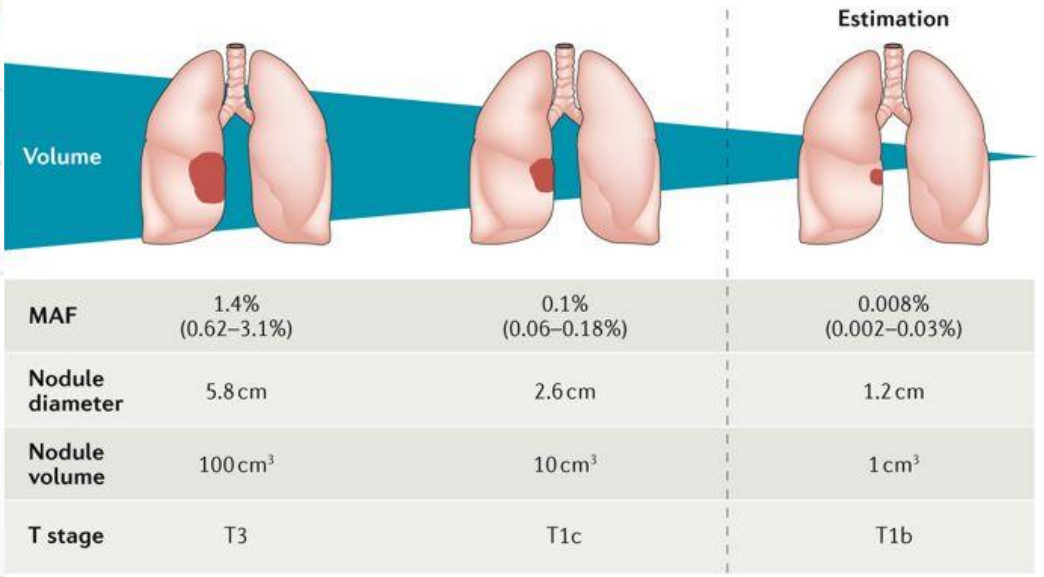


Fig. 1. Detection of ctDNA in patients with NSCLC

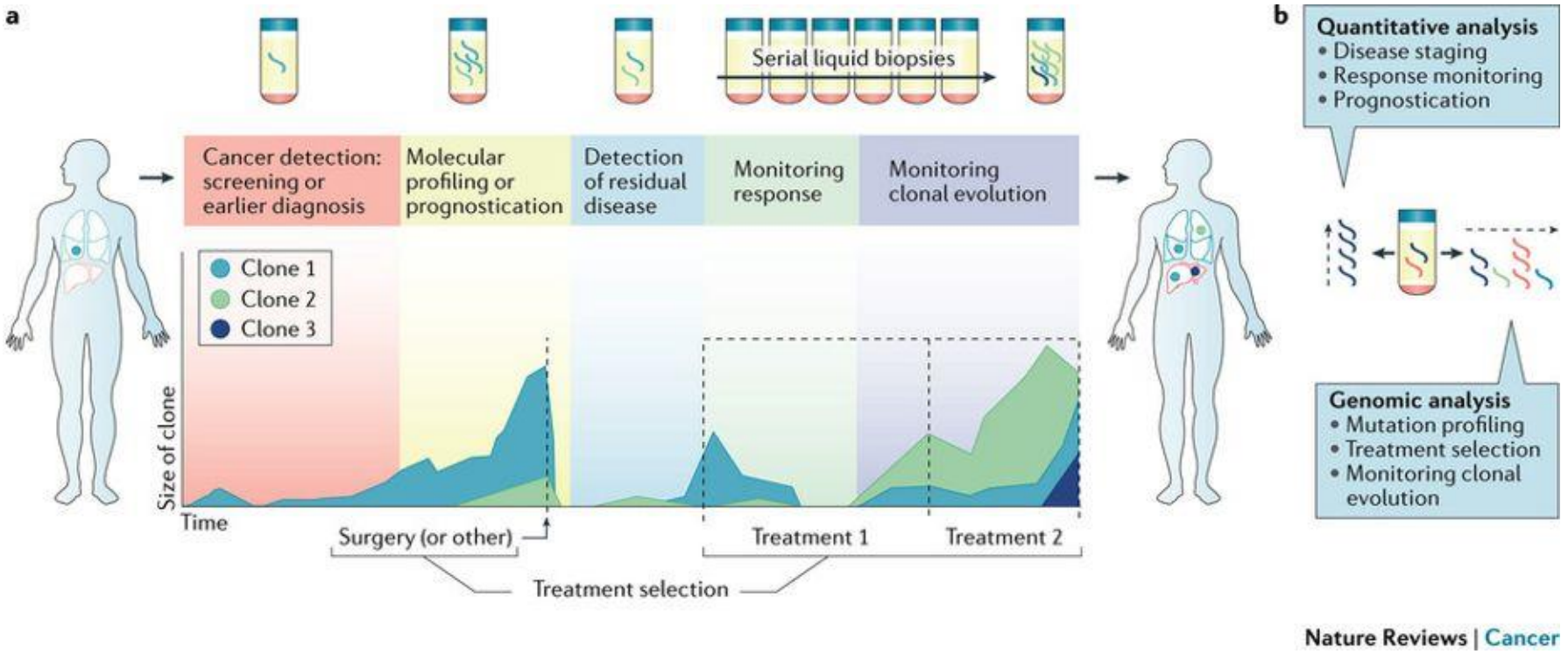


MAF	1.4% (0.62–3.1%)	0.1% (0.06–0.18%)	0.008% (0.002–0.03%)
Nodule diameter	5.8 cm	2.6 cm	1.2 cm
Nodule volume	100 cm^3	10 cm^3	1 cm^3
T stage	T3	T1c	T1b

Fig. 3. The correlation between the abundance of ctDNA, tumour volume, tumour diameter, and T stage.

Nature Reviews Clinical Oncology 2018;15:577–586

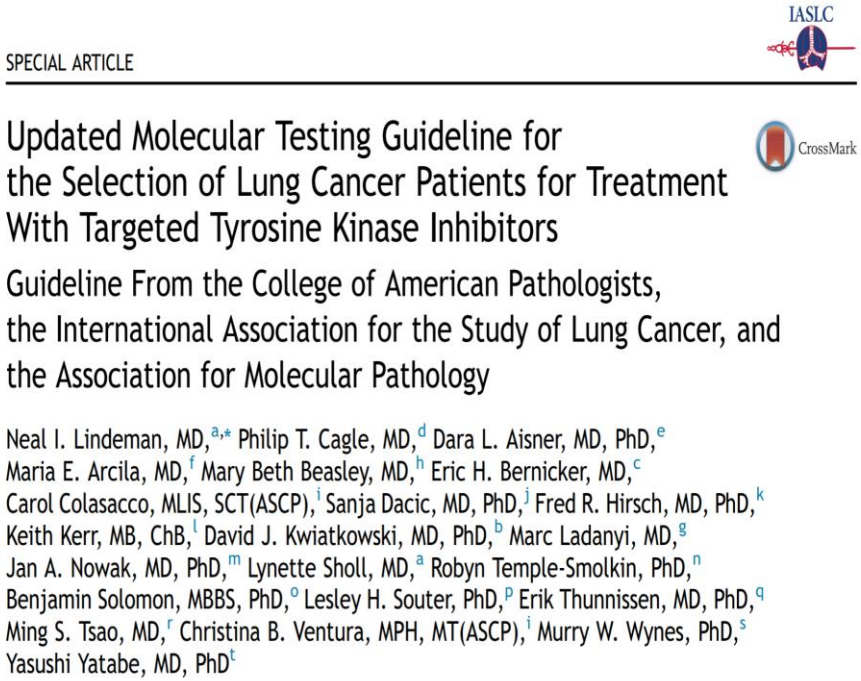
Liquid biopsies come of age
: towards implementation of circulating tumour DNA



Nature Reviews Cancer 2017;17:223–238

Advanced Lung Cancer…

…Doing more with less



SPECIAL ARTICLE

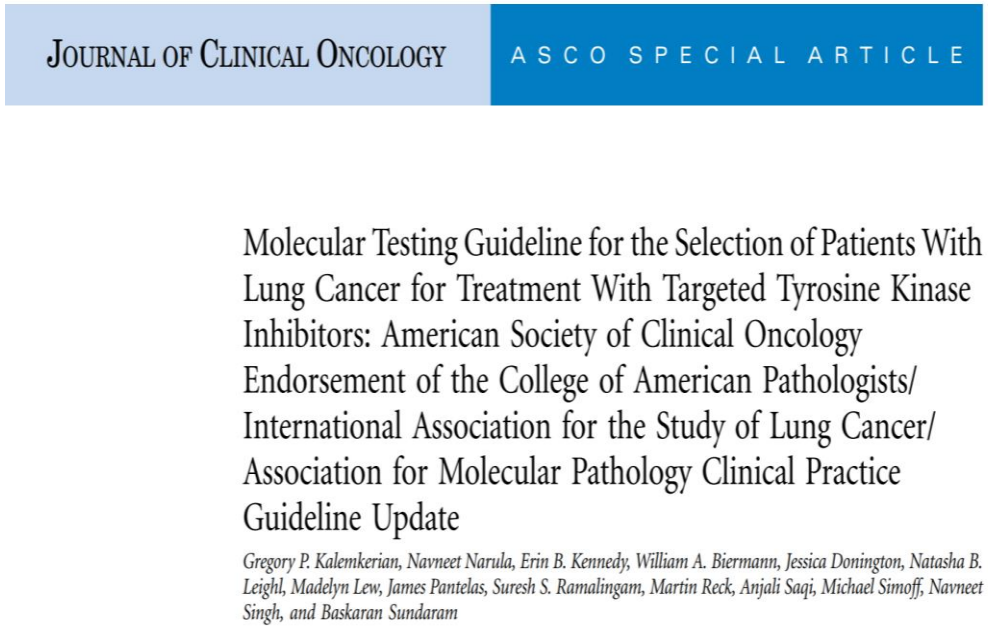
IASLC

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,[d] Dara L. Aisner, MD, PhD,[e] Maria E. Arcila, MD,[f] Mary Beth Beasley, MD,[h] Eric H. Bernicker, MD,[c] 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,[g] 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]

J Thorac Oncol 2018 Mar 13(3):323-358



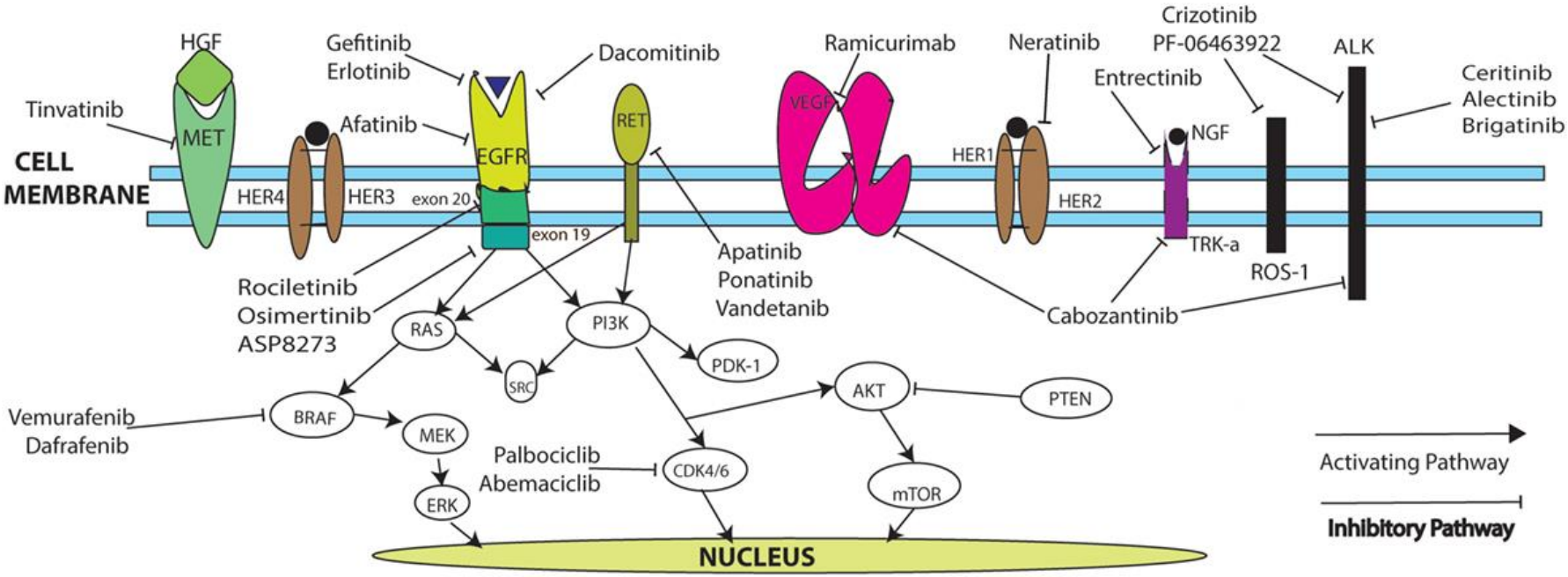
JOURNAL OF CLINICAL ONCOLOGY | ASCO SPECIAL ARTICLE

Molecular Testing Guideline for the Selection of Patients With Lung Cancer for Treatment With Targeted Tyrosine Kinase Inhibitors: American Society of Clinical Oncology Endorsement of the College of American Pathologists/ International Association for the Study of Lung Cancer/ Association for Molecular Pathology Clinical Practice Guideline Update

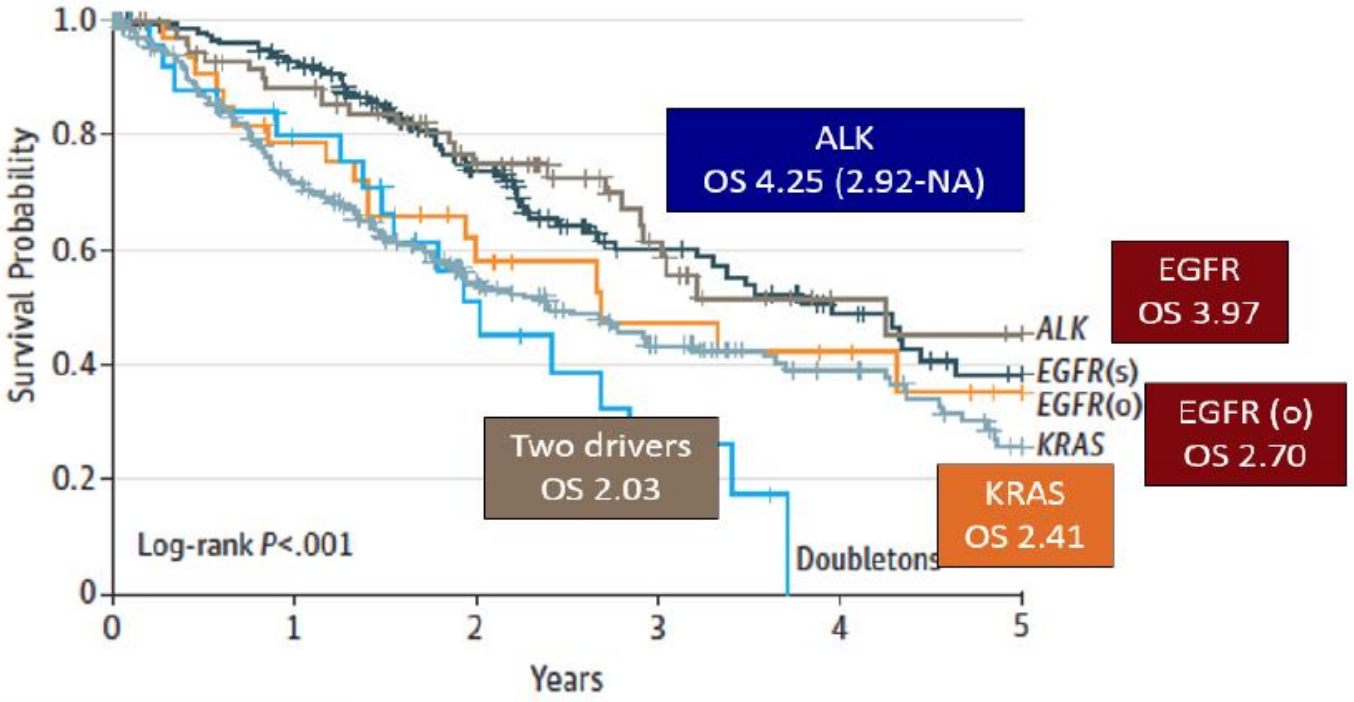
Gregory P. Kalemkerian, Navneet Narula, Erin B. Kennedy, William A. Biermann, Jessica Donington, Natasha B. Leighl, Madelyn Lew, James Pantelas, Suresh S. Ramalingam, Martin Reck, Anjali Saqi, Michael Simoff, Navneet Singh, and Baskaran Sundaram

J Clin Oncol. 2018 Mar 20;36(9):911-919

Targeted Therapy for Oncogenic Driver



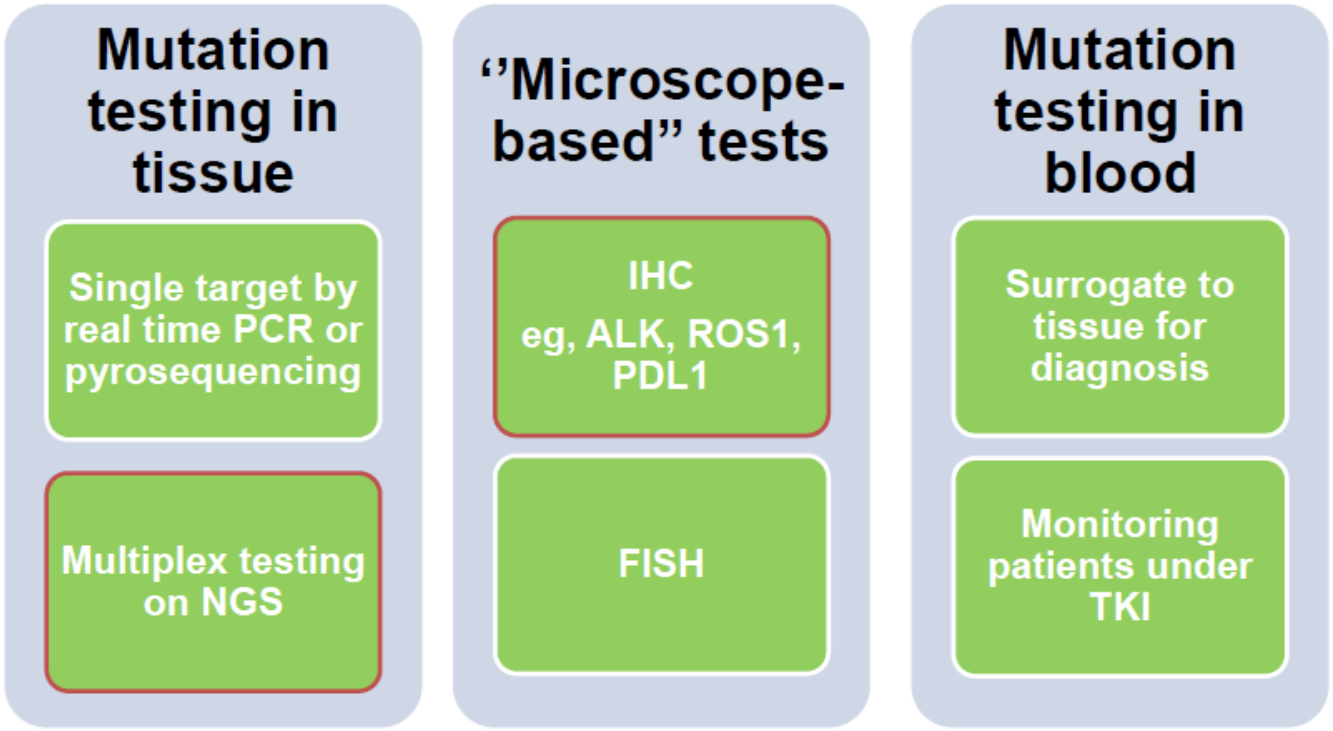
Targeted Therapy Improves Outcomes in Patients with Oncogenic Driver Mutations



EGFR, epidermal growth factor receptor; OS, overall survival

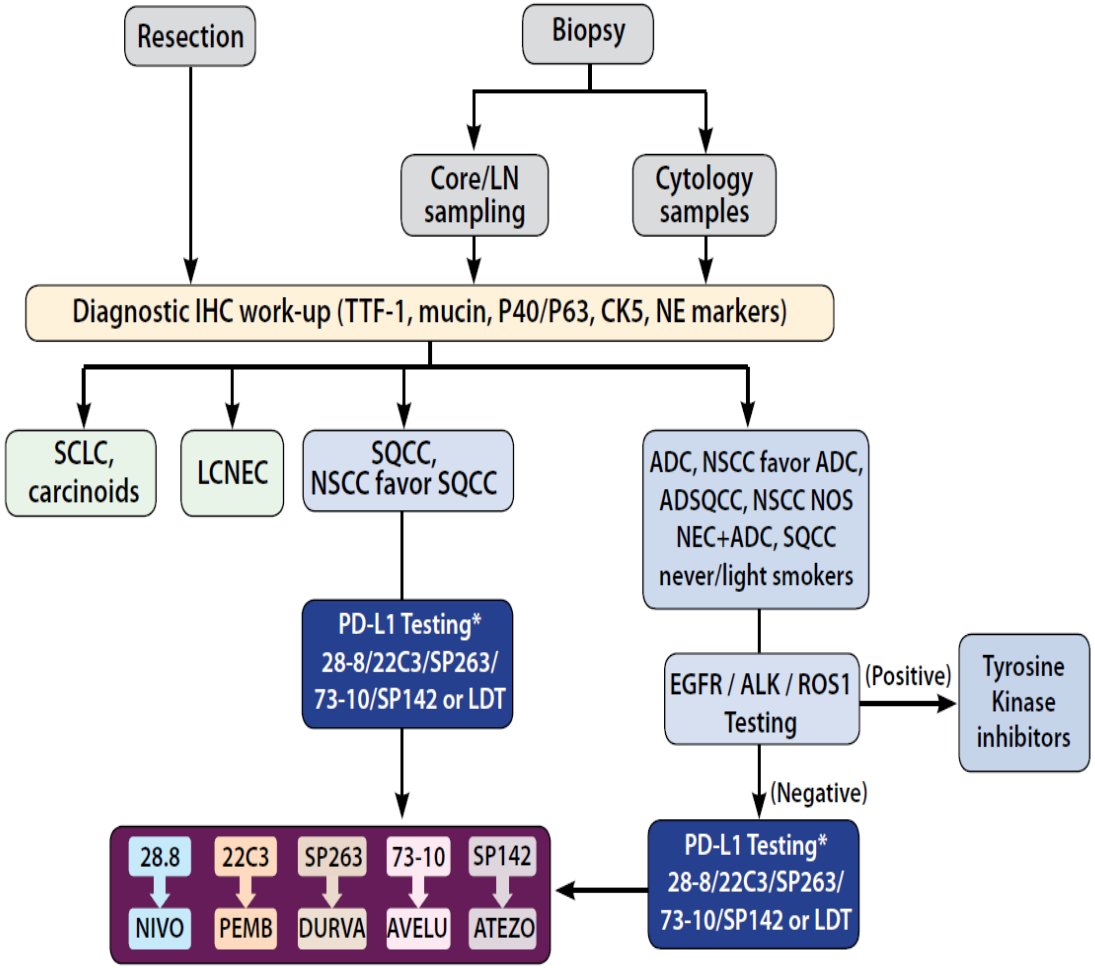
Kris MG, et al. *JAMA*. 2014;311(19):1998-2006.

Molecular Profiling of NSCLC in Routine Practice



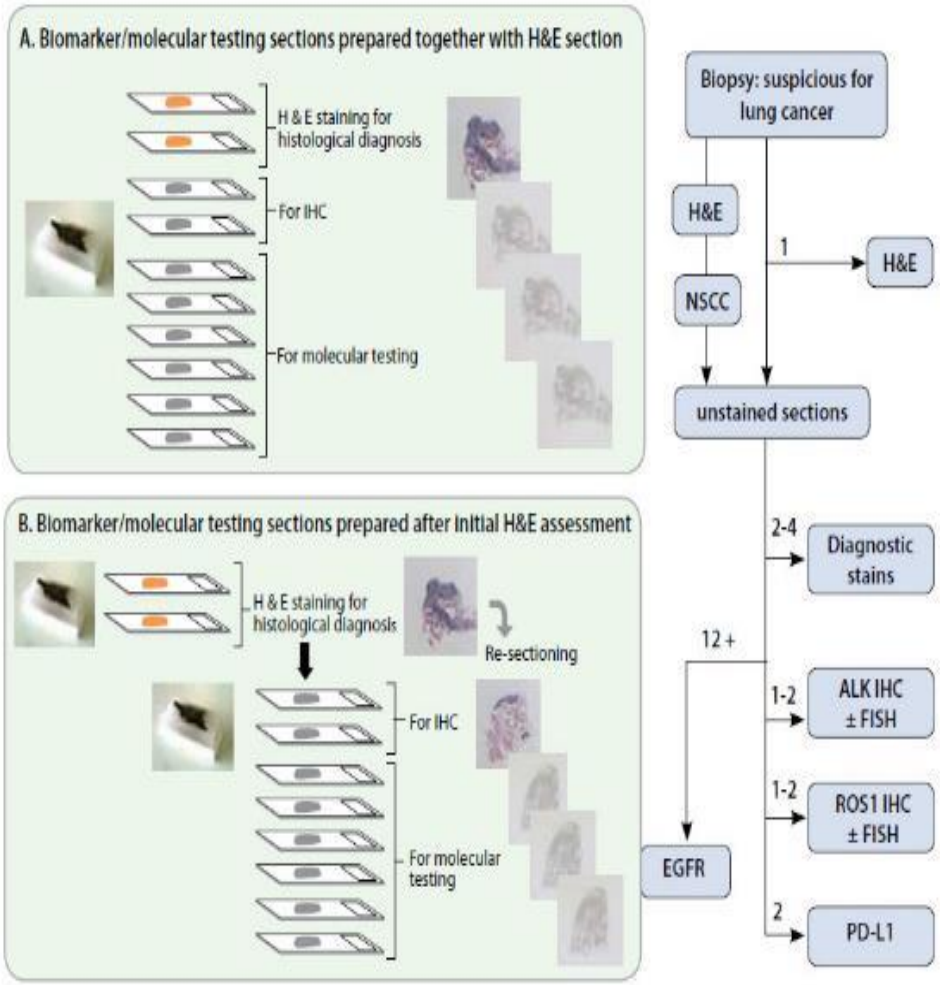
FISH, fluorescence *in situ* hybridization; IHC, immunohistochemistry; NGS, next-generation sequencing; PCR, polymerase chain reaction; TKI, tyrosine kinase inhibitor

IHC tests that are integral to diagnostic considerations in the treatment of patients with lung cancer



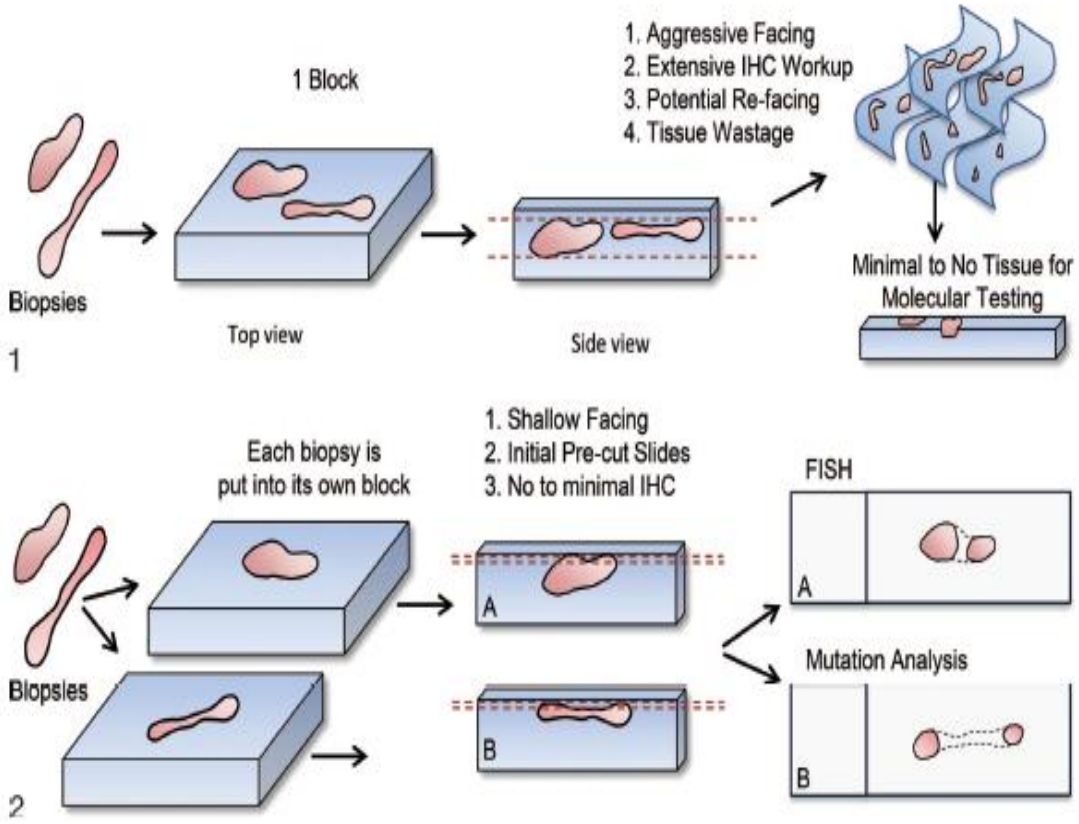
Tsao et al., IASLC ATLAS OF **PD-L1** IMMUNOHISTOCHEMISTRY TESTING IN LUNG CANCER 2017

Tissue Stewardship in Biomarker Testing



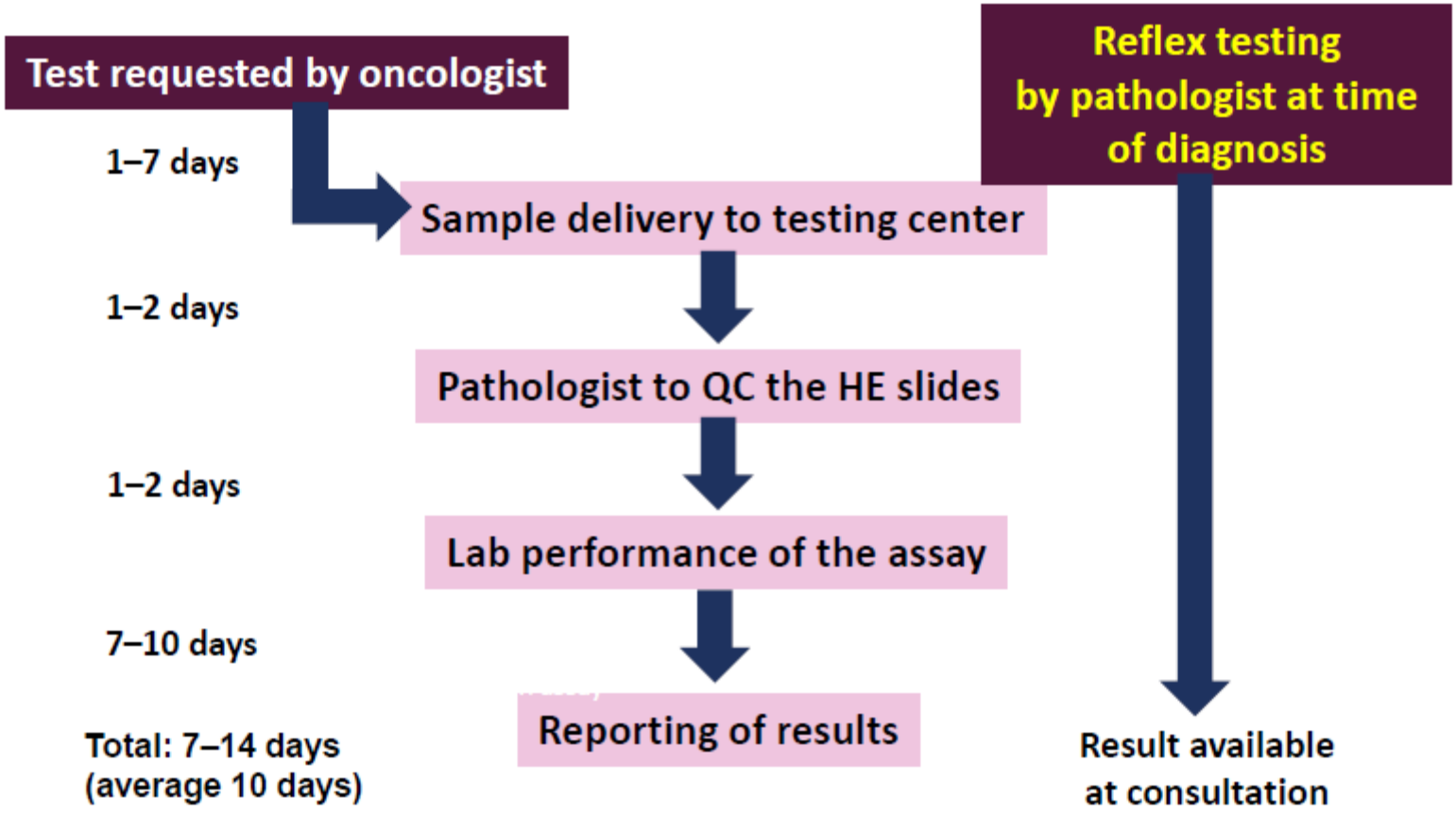
Tsao et al., IASLC ATLAS OF **PD-L1** IMMUNOHISTOCHEMISTRY TESTING IN LUNG CANCER 2017

Special Handling for Molecular Prioritization



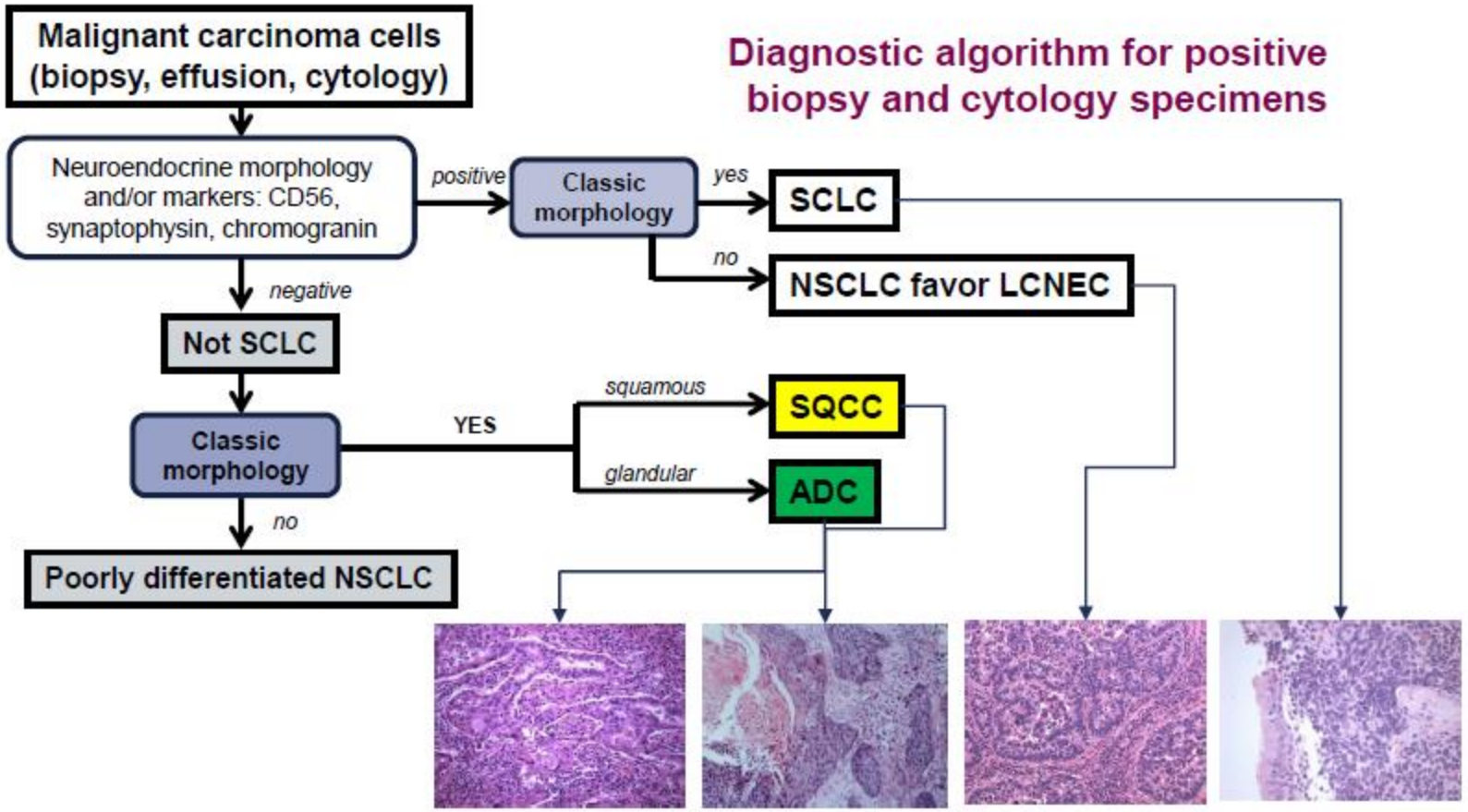
Aisner et al. Arch Pathol Lab Med 2016

Testing: Bespoke vs. Reflex



Tsao MS in ELCC2018

Diagnostic algorithm for positive biopsy and cytology specimens



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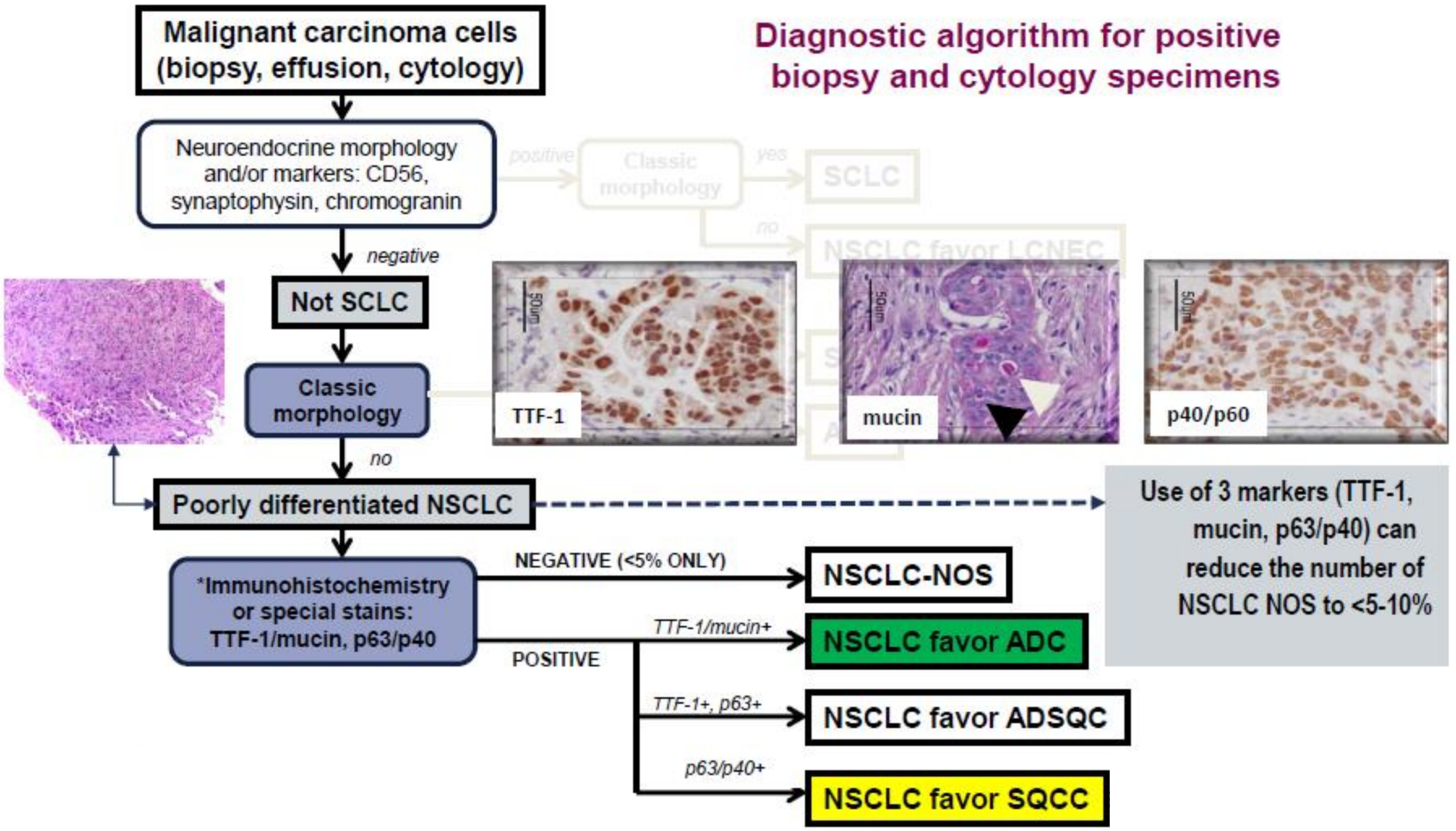
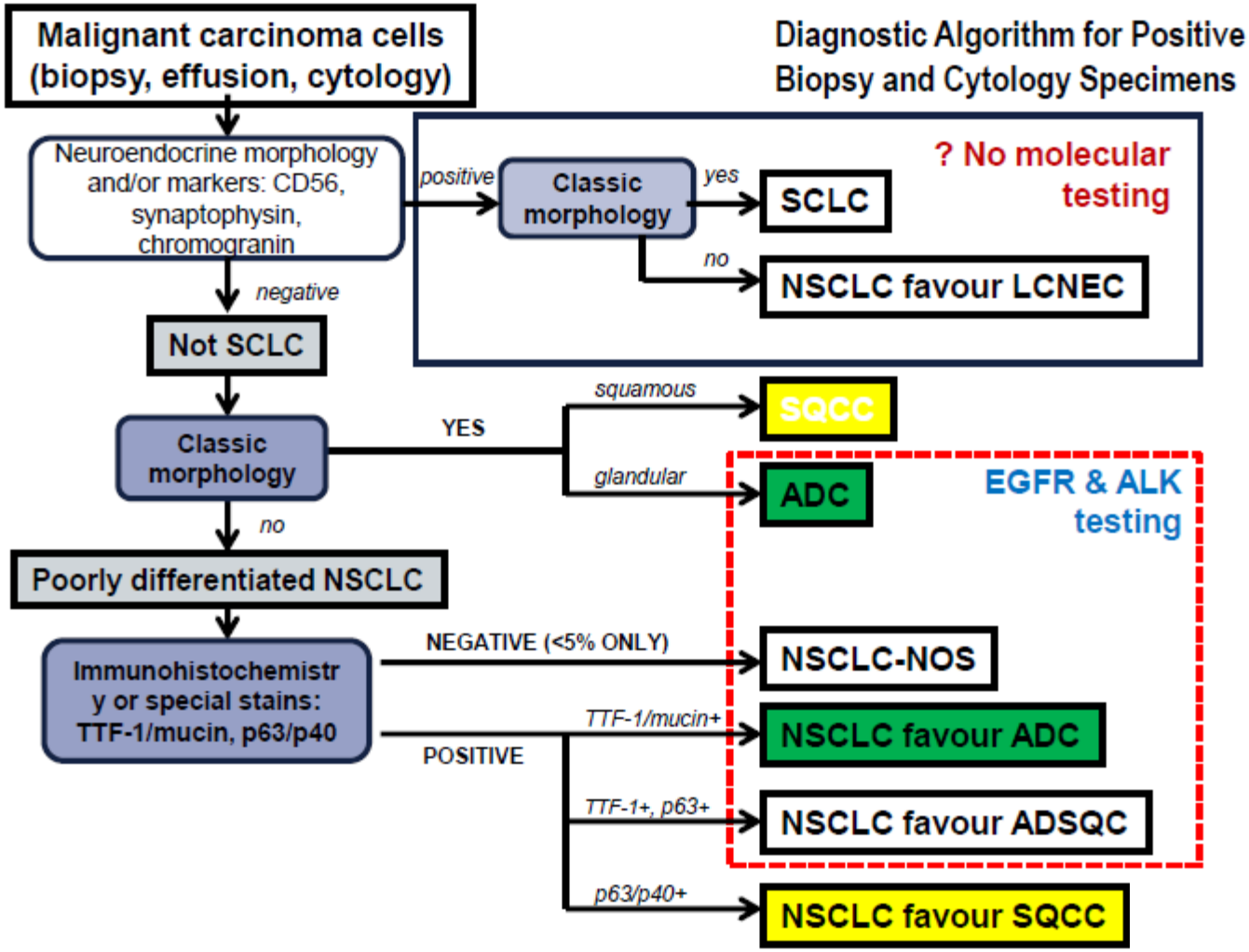
Diagnostic algorithm for positive biopsy and cytology specimens



Tsao MS in ELCC2018



Tsao MS in ELCC2018

NCCN Guidelines Version 3.2019
Non-Small Cell Lung Cancer

NCCN Guidelines Index
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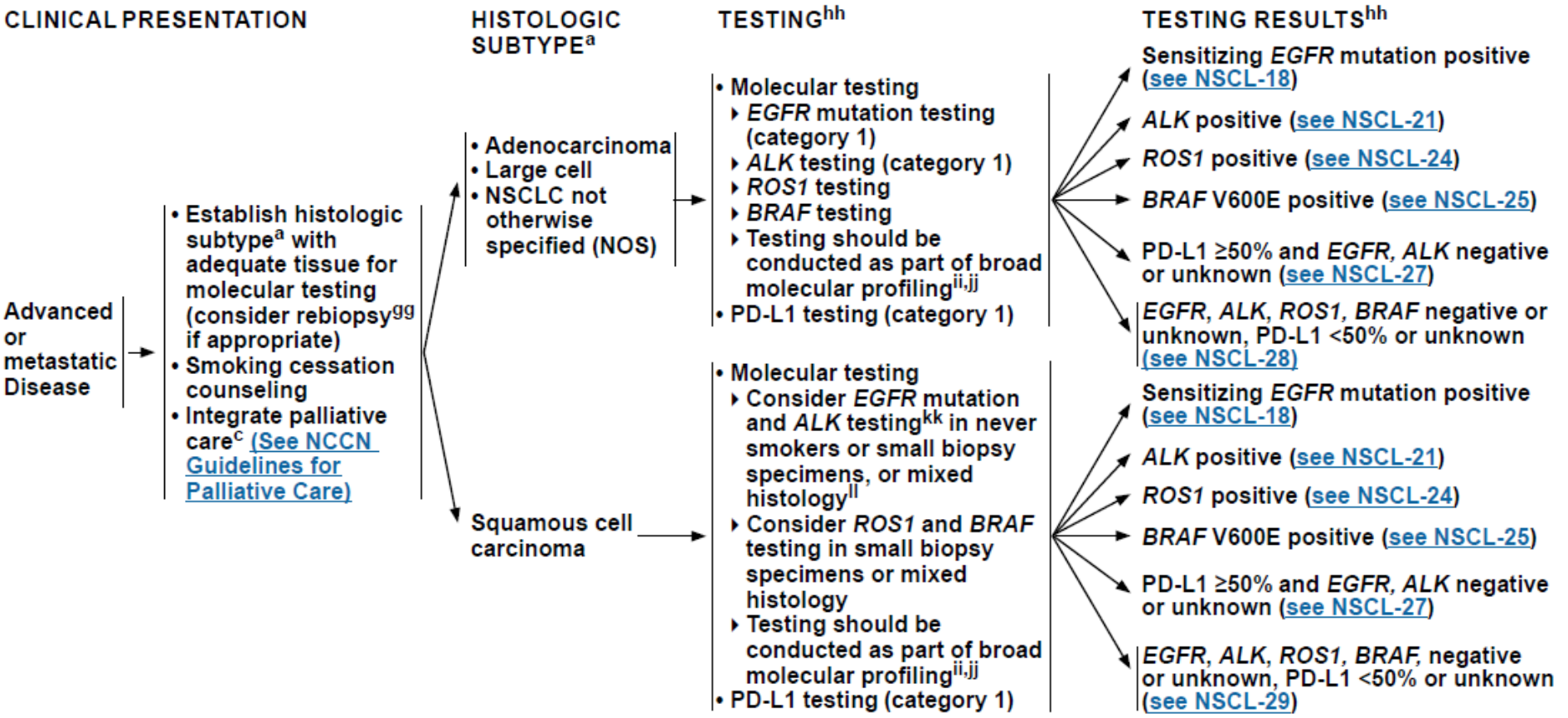
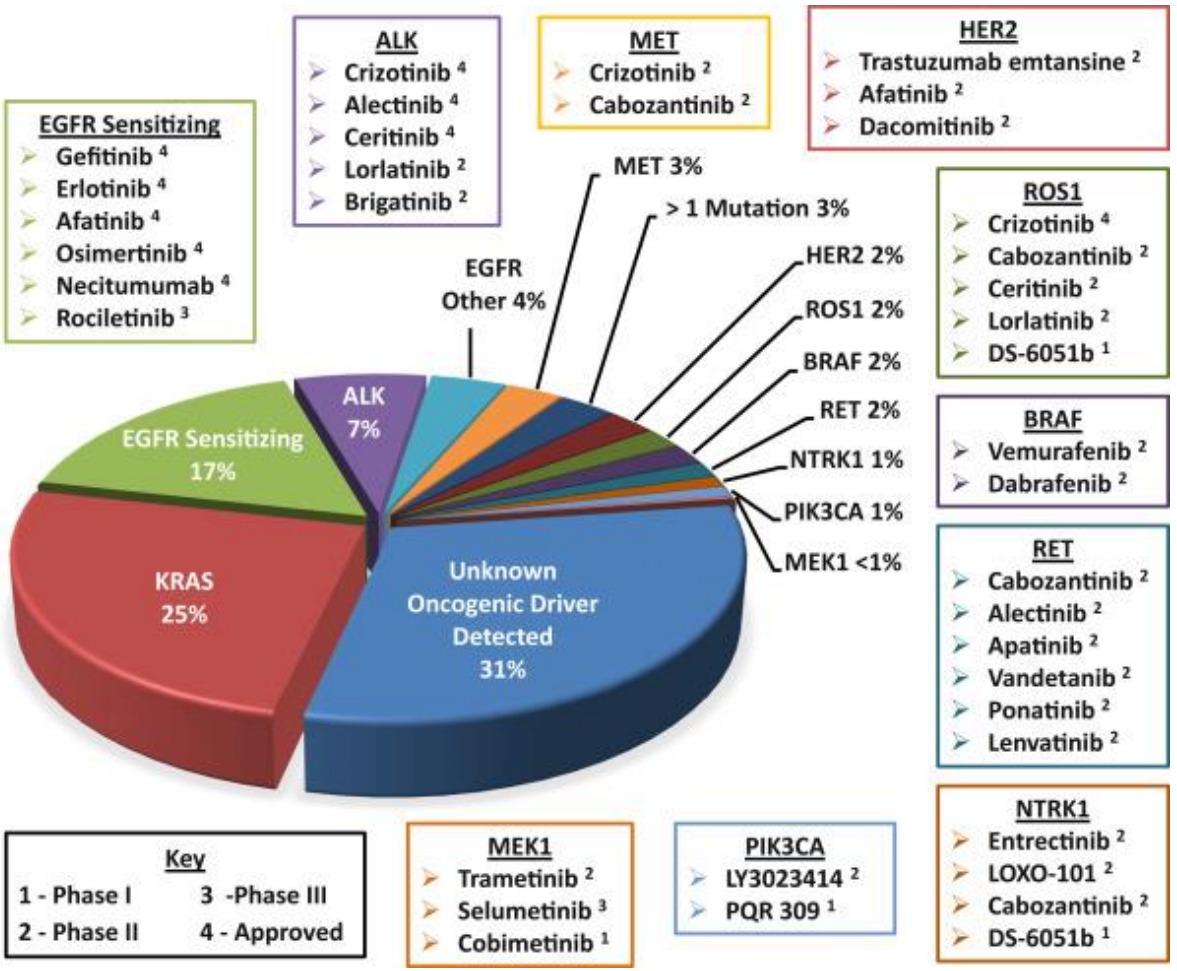
Discussion



Targeted Therapy Options Are Expanding Beyond *EGFR, ALK, ROS1* and *BRAF*



* Testing for *MET* and *HER2* should include: *MET* exon14 skipping mutation and *MET* amplification; *HER2* mutation and *HER2* amplification

Tsao AS, et al. *J Thorac Oncol*. 2016;11(5):613-638.

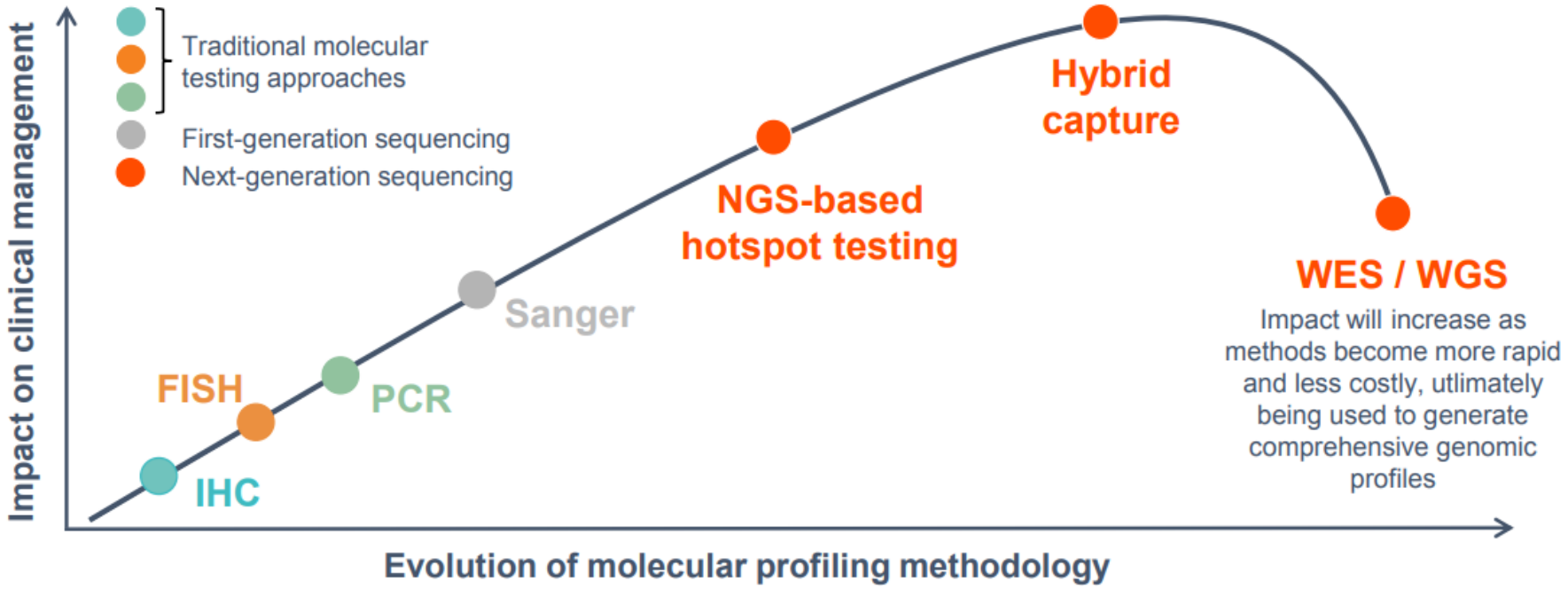
EMERGING BIOMARKERS TO IDENTIFY NOVEL THERAPIES FOR PATIENTS WITH METASTATIC NSCLC

Genetic Alteration (ie, Driver event)	Available Targeted Agents with Activity Against Driver Event in Lung Cancer
High-level *MET* amplification or *MET* exon 14 skipping mutation	Crizotinib[1-5]
RET rearrangements	Cabozantinib[6,7] Vandetanib[8]
ERBB2 (HER2) mutations	Ado-trastuzumab emtansine[9]
Tumor mutational burden (TMB)*	Nivolumab + ipilimumab[10] Nivolumab[11]

*TMB is an evolving biomarker that may be helpful in selecting patients for immunotherapy. There is no consensus on how to measure TMB.

The Evolution of Molecular Testing

Breathtaking progress in clinical managment



FISH: fluorescence in situ hybridisation; IHC: immunohistochemistry; NGS: next-generation sequencing; PCR: polymerase chain reaction; WES: whole exome sequencing; WGS: whole genome sequencing.

Netto, G.J. et al. *Proc Bayl Univ Med Cent* 2003;16:379-83.

de Matos, L.L, et al. *Biomark Insights* 2010;5:9-20.

Dong, L., et al. *Curr Genomics* 2015;16:253-63.

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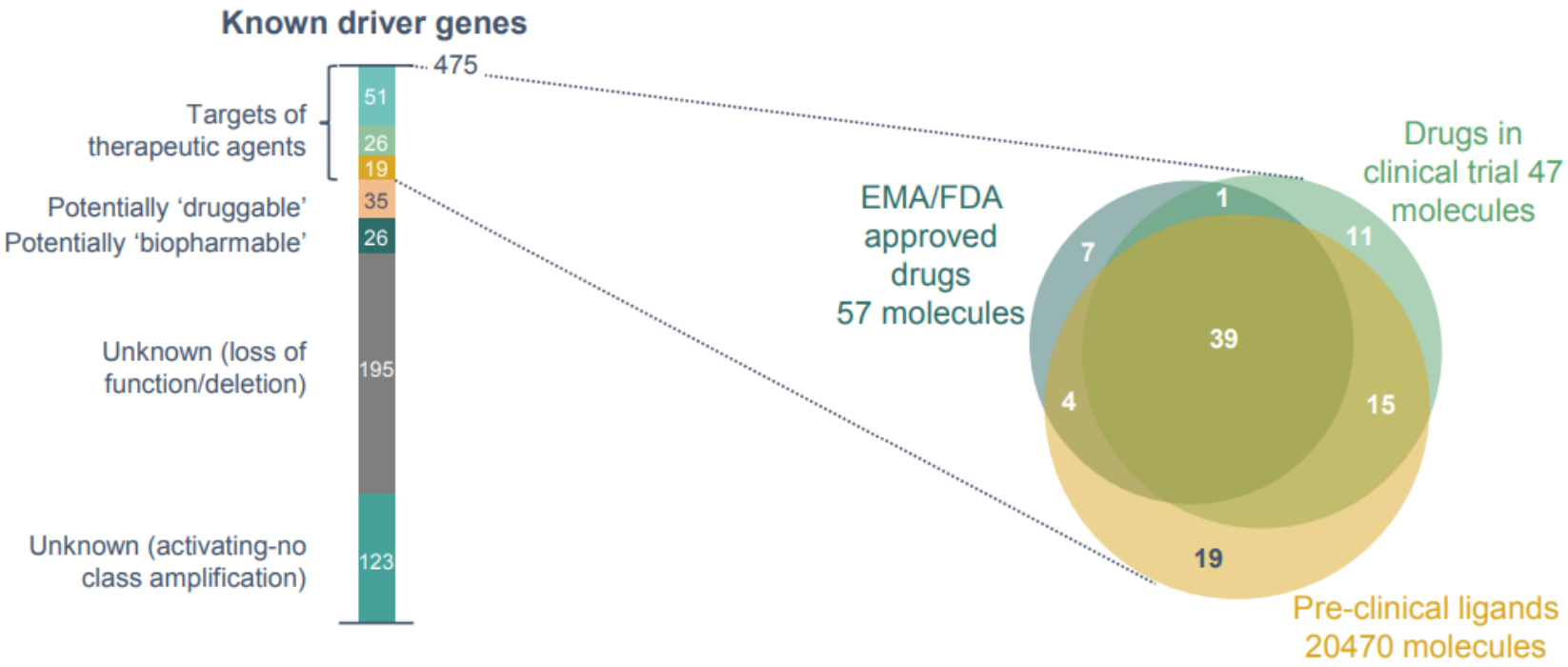
Access to therapy: only ~20% of known driver genes have an associated therapy



Adapted from Rubio-Perez, C., et al. (2015) Cancer Cell. 27(3):382–96.

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COMMENTARY

Updates Regarding Biomarker Testing for Non-Small Cell Lung Cancer: Considerations from the National Lung Cancer Roundtable

Edward S. Kim, MD,[a,*] Upal Basu Roy, PhD, MPH,[b] Jennifer L. Ersek, PhD, MSPH,[a] Jennifer King, PhD,[c] Robert A. Smith, PhD,[d] Nicole Martin, MA,[b] Renato Martins, MD, MPH,[e] Amy Moore, PhD,[f] Gerard A. Silvestri, MD, MS,[g] James Jett, MD[h]

Table 2. Guideline-Concordant, Recommended, and Optional Biomarkers in Patients with NSCLC

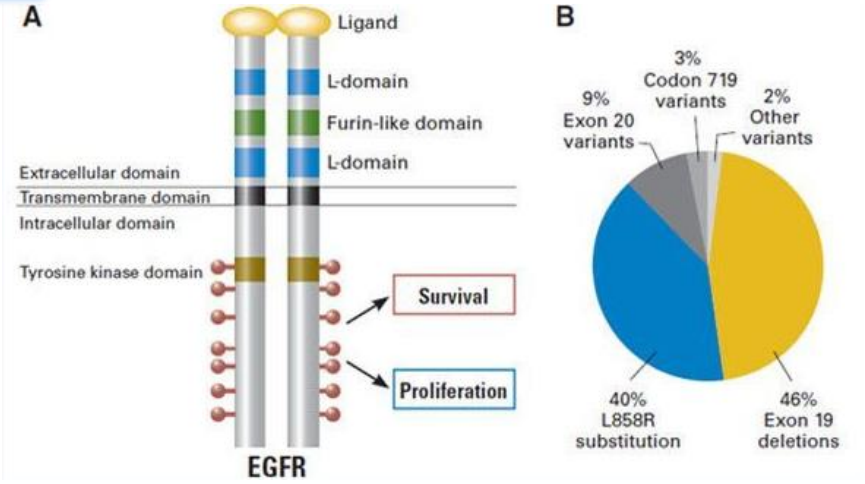
Guideline-Concordant	Recommended	Optional[a]
EGFR, including T790M		RET
ALK	MSI	MET
BRAF	PD-L1	HER2
ROS1	NTRK	
		KRAS
		TMB

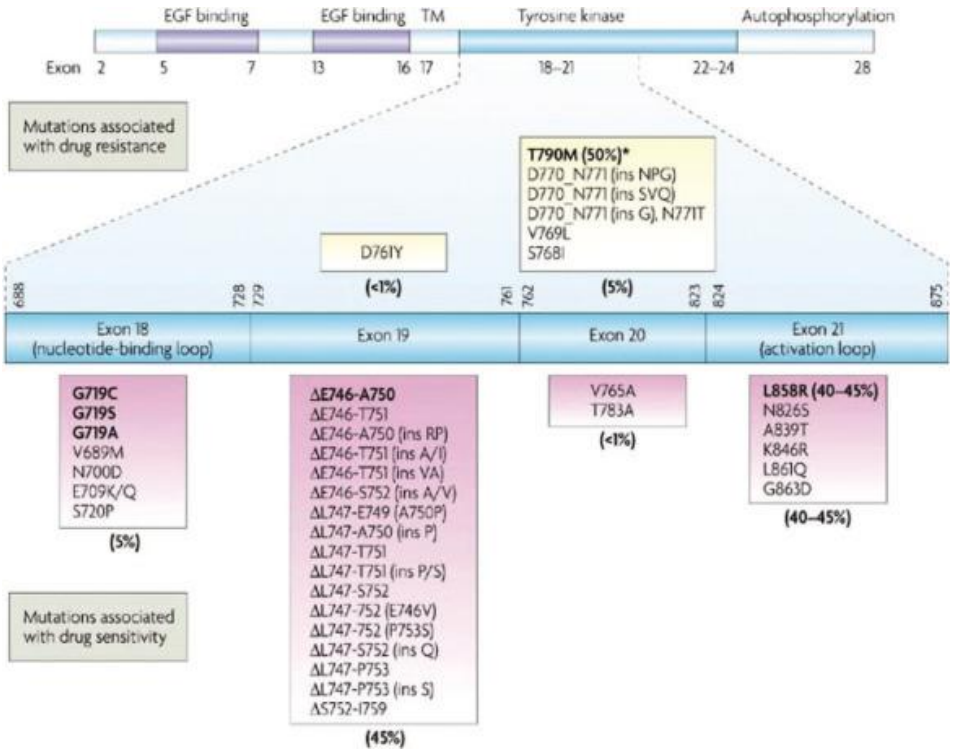
[a]These markers should be assessed as part of a large next-generation sequencing panel.

RET, ret proto-oncogene; ALK, ALK receptor tyrosine kinase; MSI, microsatellite instability; MET, MNNG-HOS transforming gene; PD-L1, programmed death ligand 1; HER2, erb-b2 receptor tyrosine kinase; TMB, tumor mutational burden.

J Thorac Oncol 2019;14(3):338-342

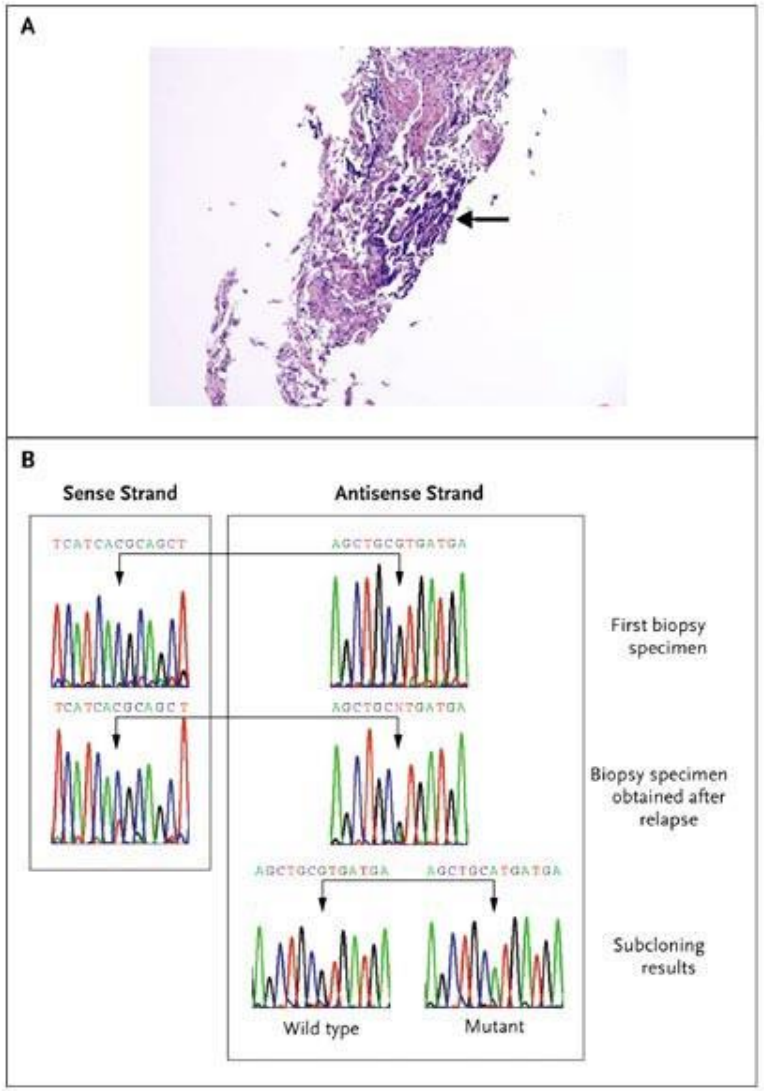
EGFR





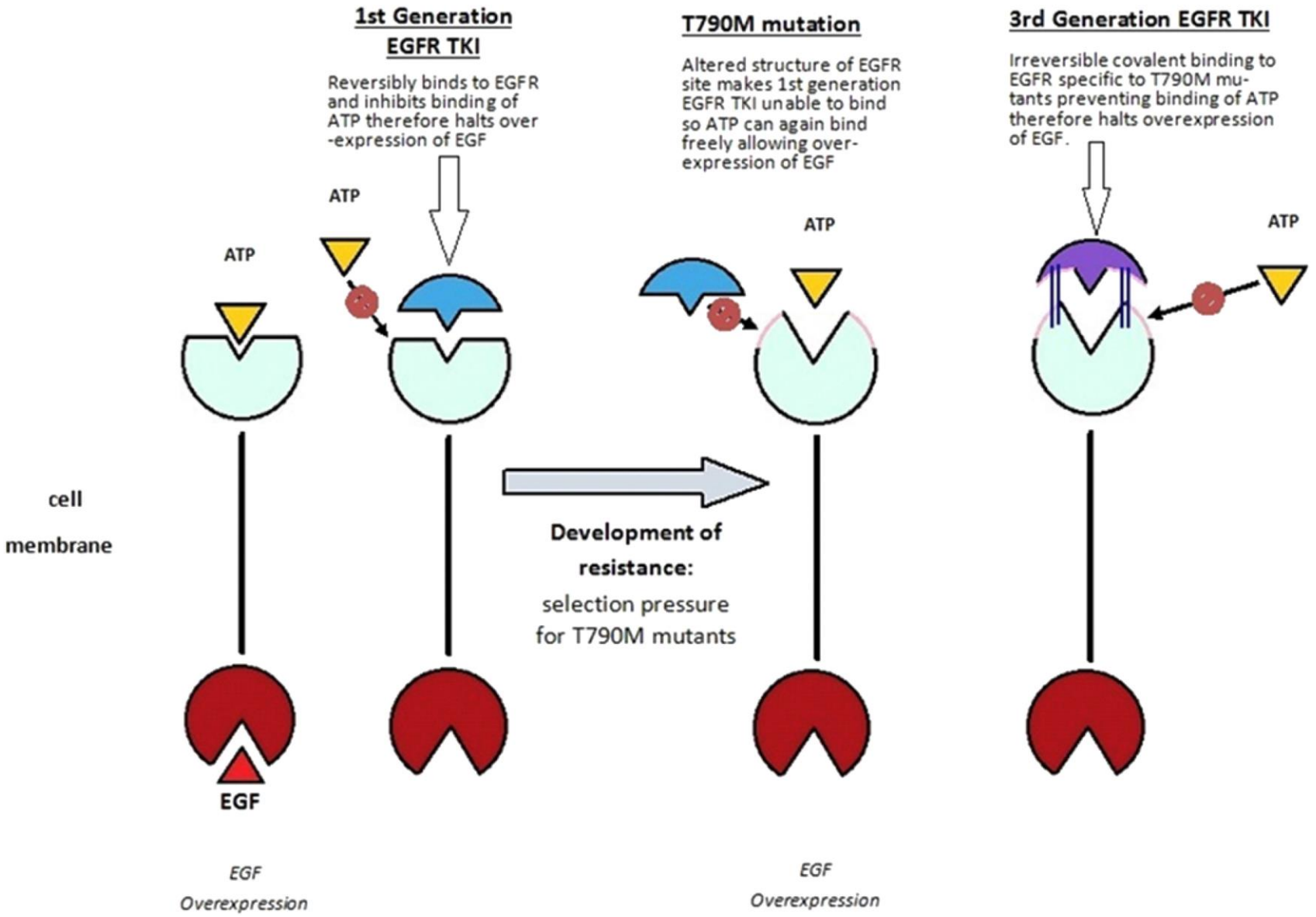
Nat Rev Cancer 2007;7:169-181

Identification of a Second *EGFR* Mutation



Kobayashi S et al. N Engl J Med 2005;352:786-792

EGFR



Respir Med Case Rep. 2017; 20: 137–140

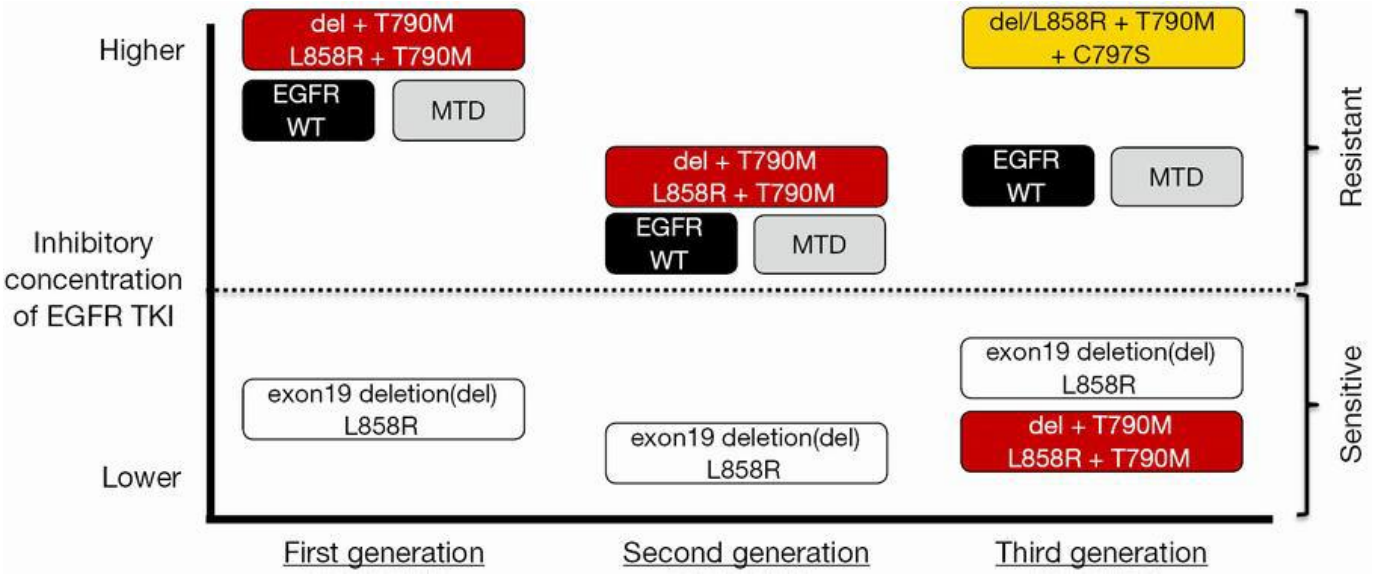
EGFR TKIs with regulatory approval

Table 1. EGFR TKIs with regulatory approval for the treatment of EGFR-mutant NSCLC

Generation	Name	Selectivity	Reversible/Irreversible	Approval status
1st	Gefitinib	WT EGFR	Reversible	FDA, EMA
	Erlotinib	WT EGFR	Reversible	FDA, EMA
	Icotinib	WT EGFR	Reversible	CFDA
2nd	Afatinib	WT EGFR	Irreversible	FDA, EMA, CFDA
3rd	Osimertinib	Mutant EGFR	Irreversible	FDA, EMA
	Olmutinib	Mutant EGFR	Irreversible	KFDA (conditional)

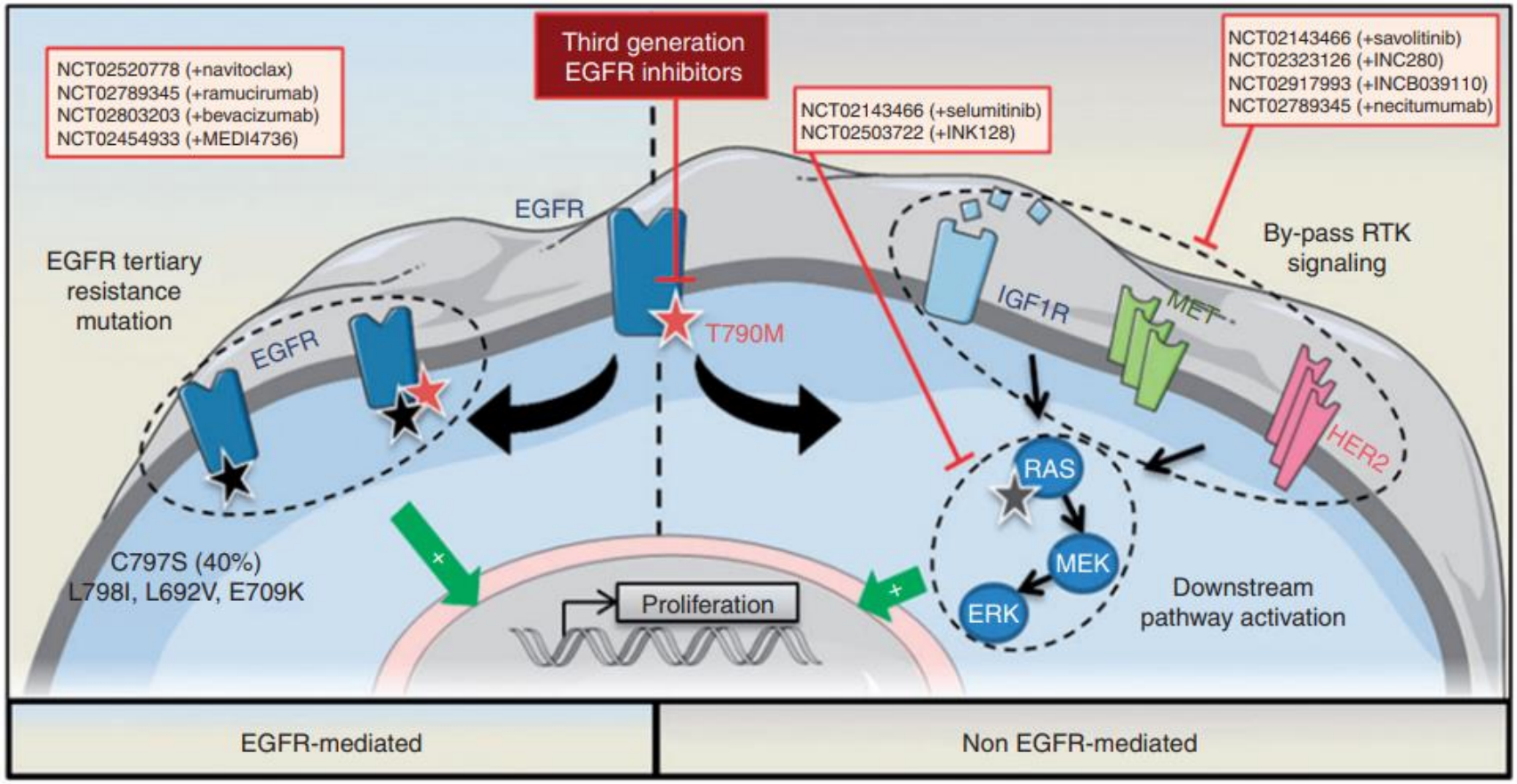
WT, wild-type; FDA, US Food and Drug Administration; EMA, European Medicines Agency; CFDA, China Food and Drug Administration; KFDA, Korea Food & Drug Administration.

Ann Oncol 2018;29(Suppl 1):i10-i19



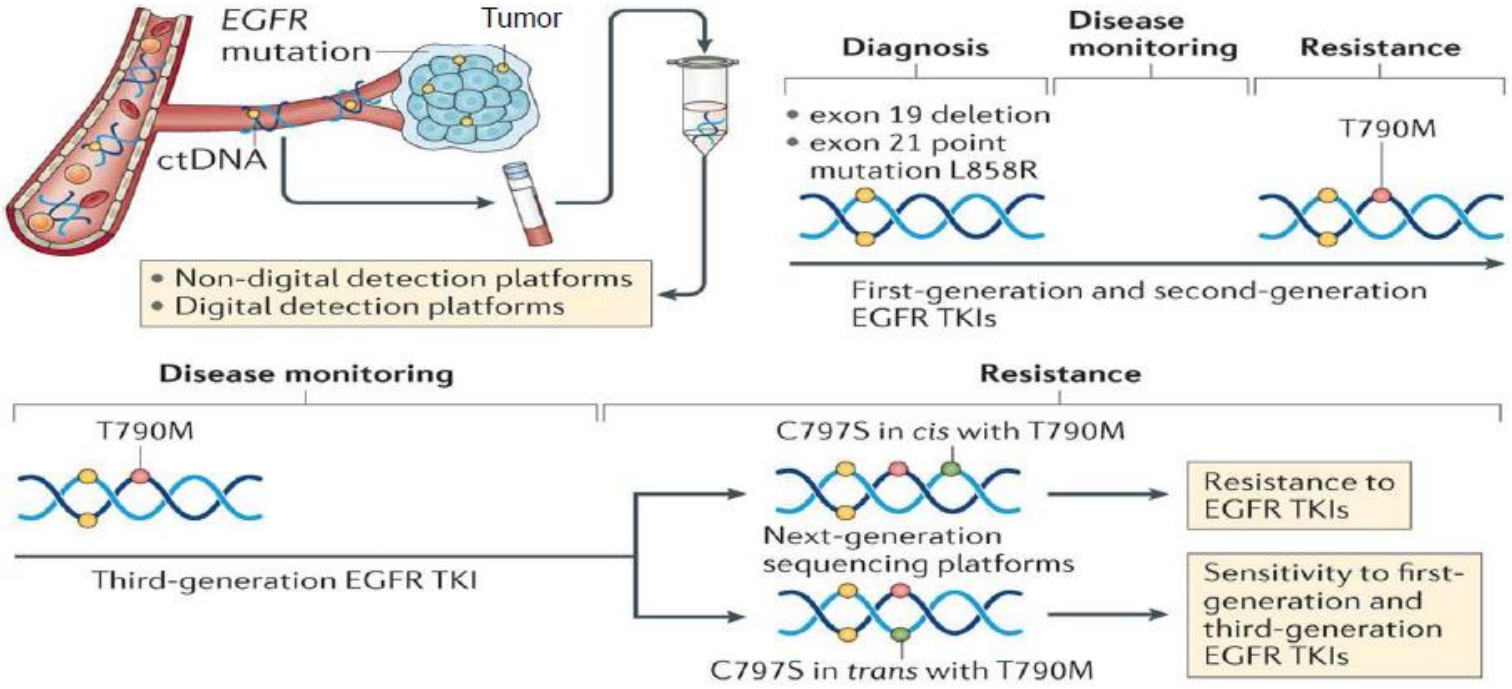
Transl Lung Cancer Res 2015;4(6):809-815

Heterogeneous resistance mechanisms to 3rd-generation EGFR-TKI



Ann Oncol 2018;29(Suppl 1):i28-i37

The Dynamic Nature of Resistance Mechanisms Can Be Monitored in ctDNA



Rosell R, et al. *Nat Rev Clin Oncol*. 2016;13(7):401-402.

PL01 - Patients First (ID 849)

Type: **Plenary Session** | Track: | Presentations: **6**

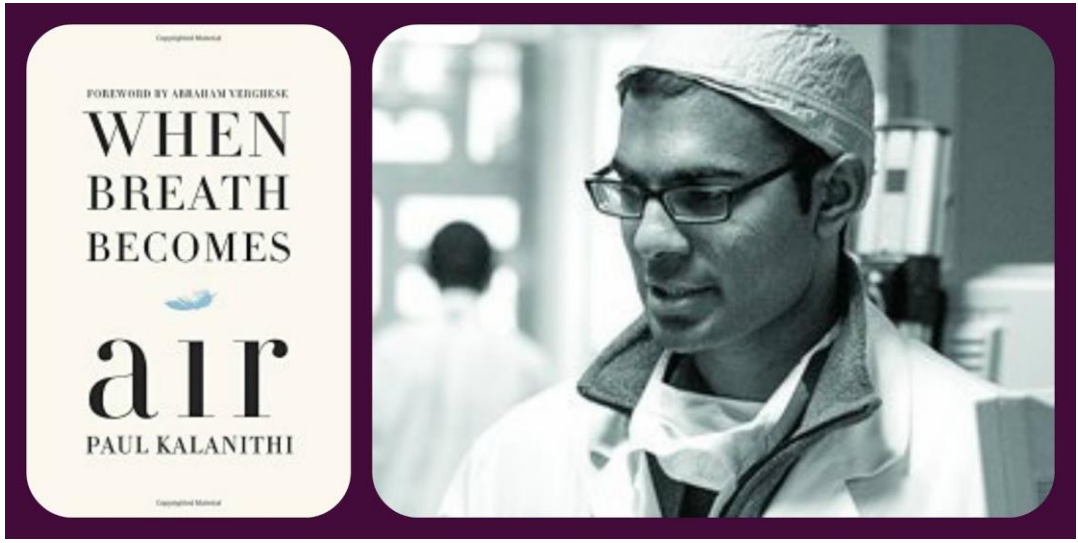
Moderators: Andrea Bezjak, Paul A. Bunn, Jr.

Coordinates: 9/24/2018, 08:15 - 09:45, Plenary Hall

+ **PL01.01 - When Breath Becomes Air (Now Available)**
08:15 - 08:25 | Presenting Author(s): Lucy Kalanithi

+ **PL01.02 - Science that Matters (Now Available)**
08:25 - 08:40 | Presenting Author(s): David P Carbone

+ **PL01.03 - Trials that Matter! (Now Available)**
08:40 - 08:55 | Presenting Author(s): Tony S. Mok



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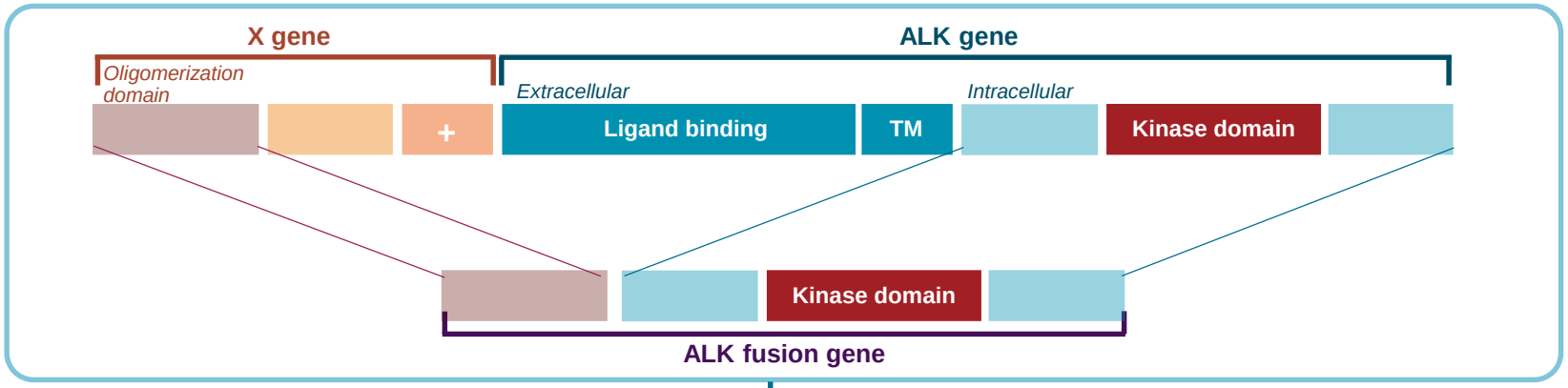
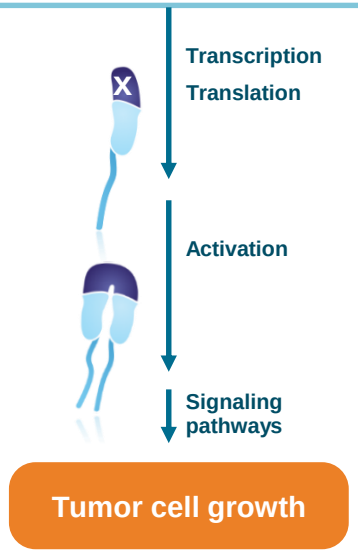
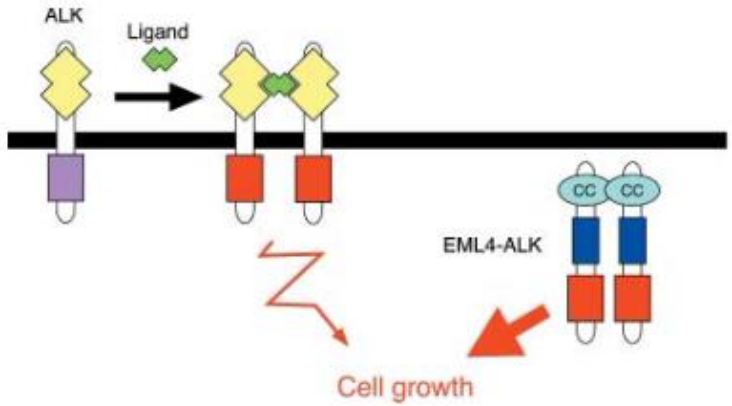
Human ALK Gene Rearrangements



- Genetic rearrangements of DNA can create novel fusion proteins[1,2]
- In the case of ALK, genetic rearrangements result in the intracellular KD of ALK fusing to the oligomerization domain of a fusion partner (X)[1,2]

"X" represents the oligomerization domain of any fusion partner that fuses with ALK.





1. Ardini E, et al. *Cancer Lett.* 2010;299:81-94.
2. Cheng M, Ott GR. *Anticancer Agents Med Chem.* 2010;10:236-249.
3. Shaw AT and Solomon B. *Clin Cancer Res.* 2011;17:2081-2086.

Hiroyuki M. *Cancer Sci* 2008; 99: 2349–2355

Diagnosis of ALK-positive NSCLC

ALK fusion gene

Transcribed into

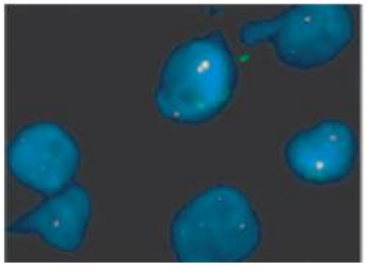
ALK fusion gene mRNA product

Translated into

ALK protein

The oncogenic effector and target of ALK TK inhibitors

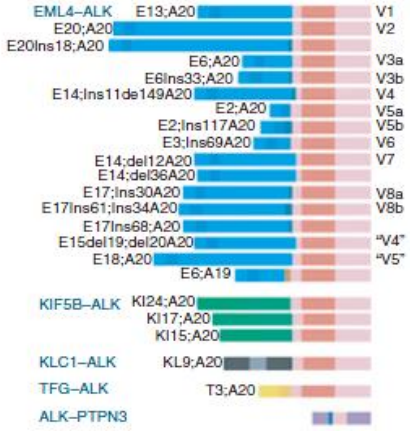
A



B

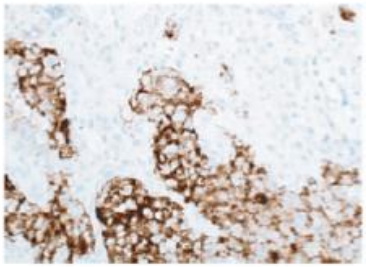
Detected by FISH or PCR

C



Detected by PCR

D



Detected by IHC

Ann Oncol 2016;27(Suppl 3):iii16-iii24

ALK

ALK FISH & immunohistochemistry assays in lung cancer

FISH: Require ≥ 15% + signals

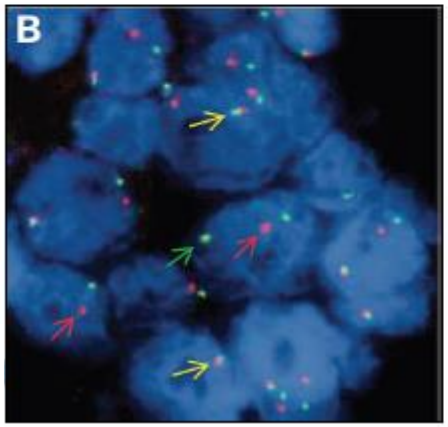
Patterns observed in split 3'-5' *ALK*

Red and green separated by ≥2 signal diameters

Classified as positive

Red and green separated by <2 signal diameters

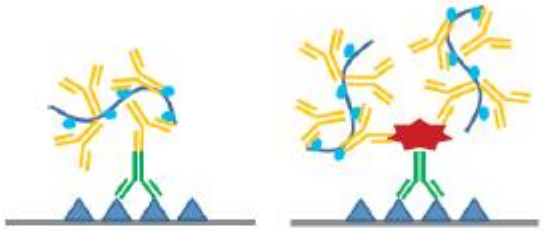
Classified as negative



IHC: Require amplification

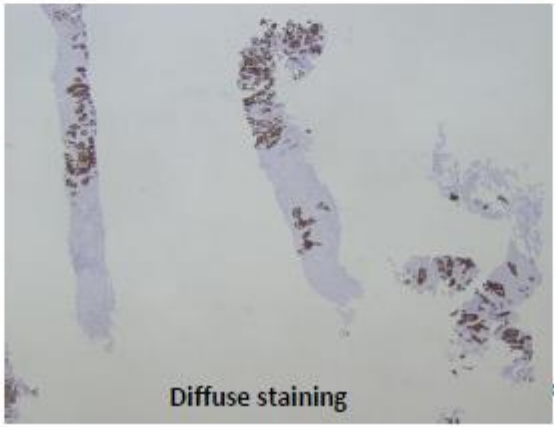
Regular Polymer Method

Linker-Polymer Method



D5F3

5A4



2013 CAP/IASLC/AMP guideline:

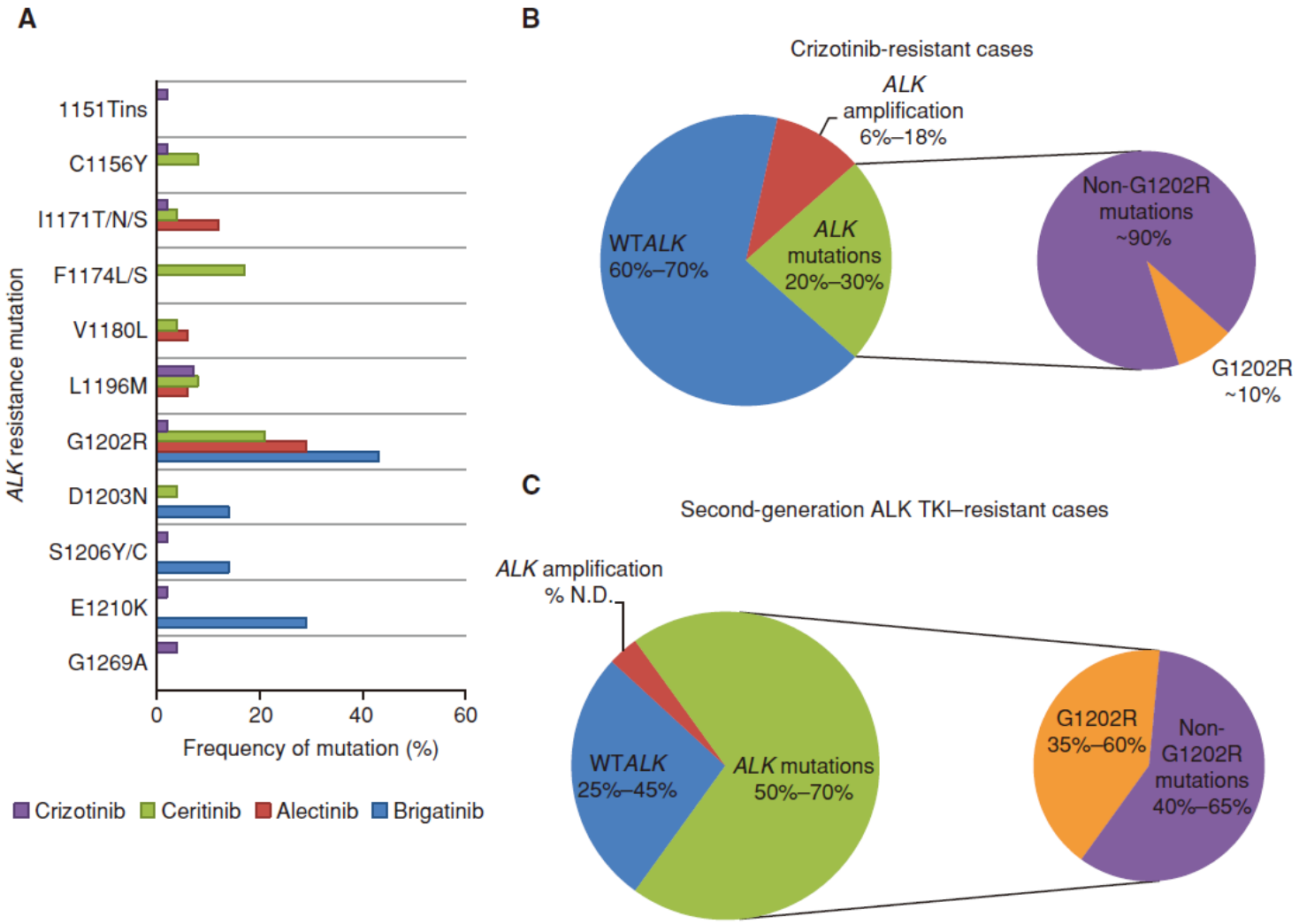
- FISH is the recommended test
- Validated IHC assay may be used as screening for FISH testing
- RT-PCR is not recommended

Tsao MS in ELCC2018

- **FISH break-apart probe** methodology was the first methodology deployed widely.
- **IHC** can be deployed as an effective screening strategy. **FDA-approved IHC (ALK[D5F3] CDx assay)** can be utilized as a standard-alone test, not requiring confirmation by FISH, although confirmation is encouraged.
- Numerous **NGS methodologies** can detect *ALK* fusions, and **targeted real-time PCR assays** are utilized in some settings, although they are unlikely to detect fusions with novel partners

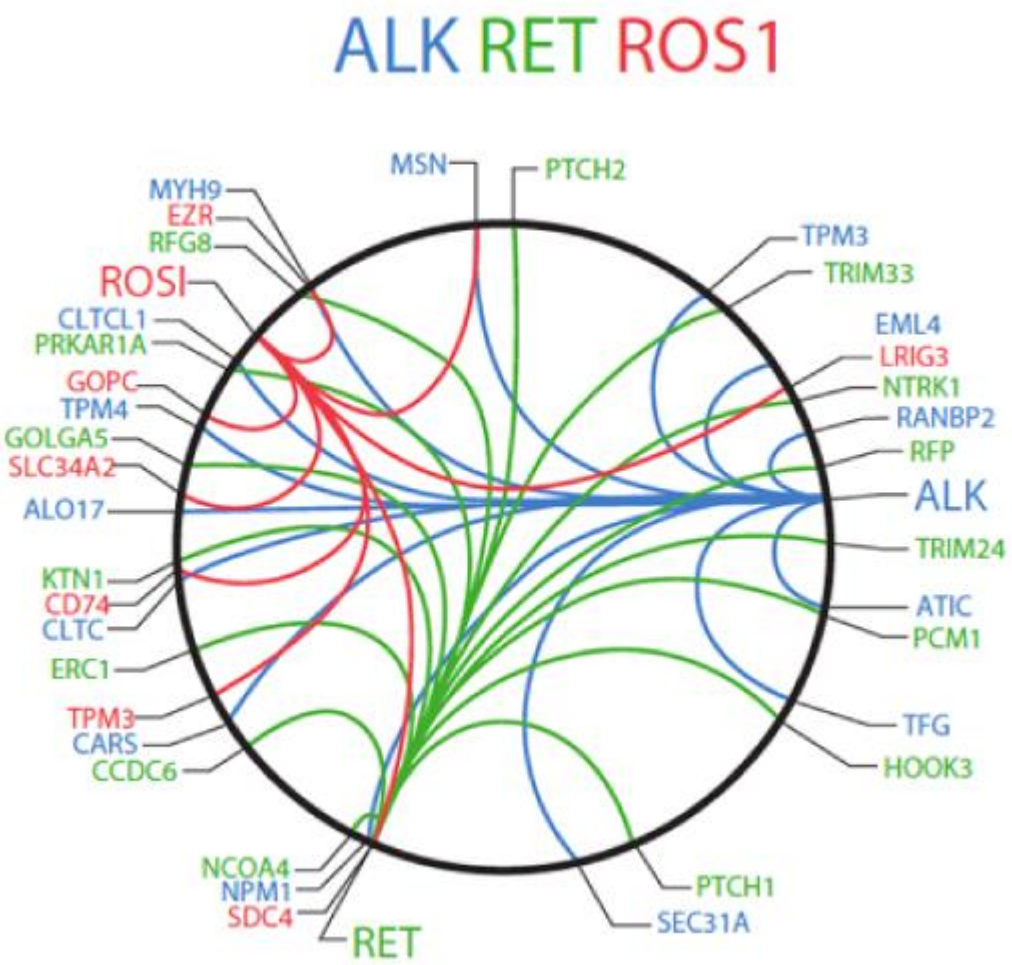
NCCN 2019

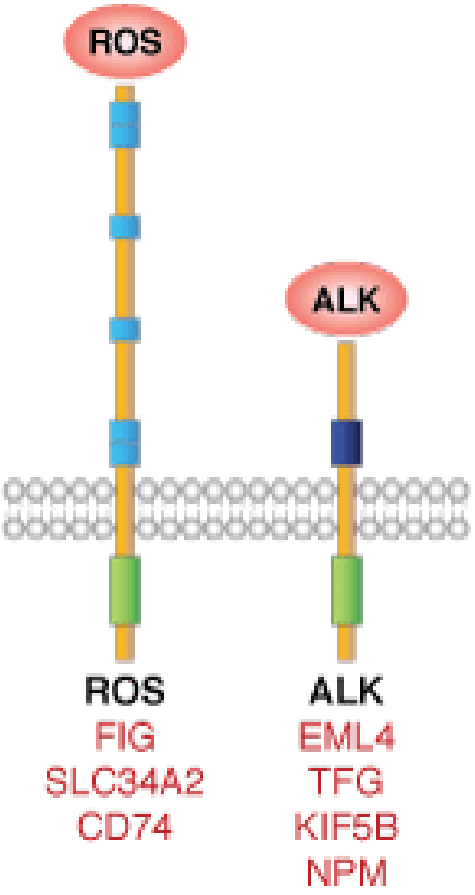
Mechanism of Acquired Resistance to ALK Inhibitors



Cancer Discov 2017;7(2):1-19

ROS1

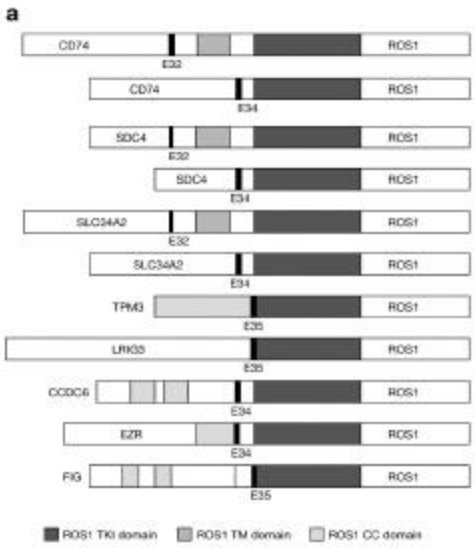


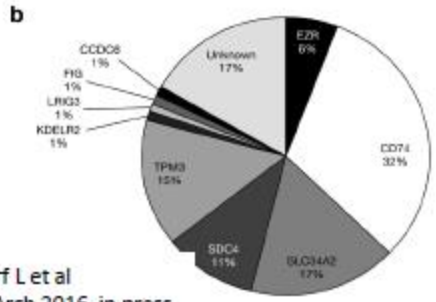


https://archerdx.com/company/blog/applications/cancer-and-alk,-ret,-ros1-gene-fusions

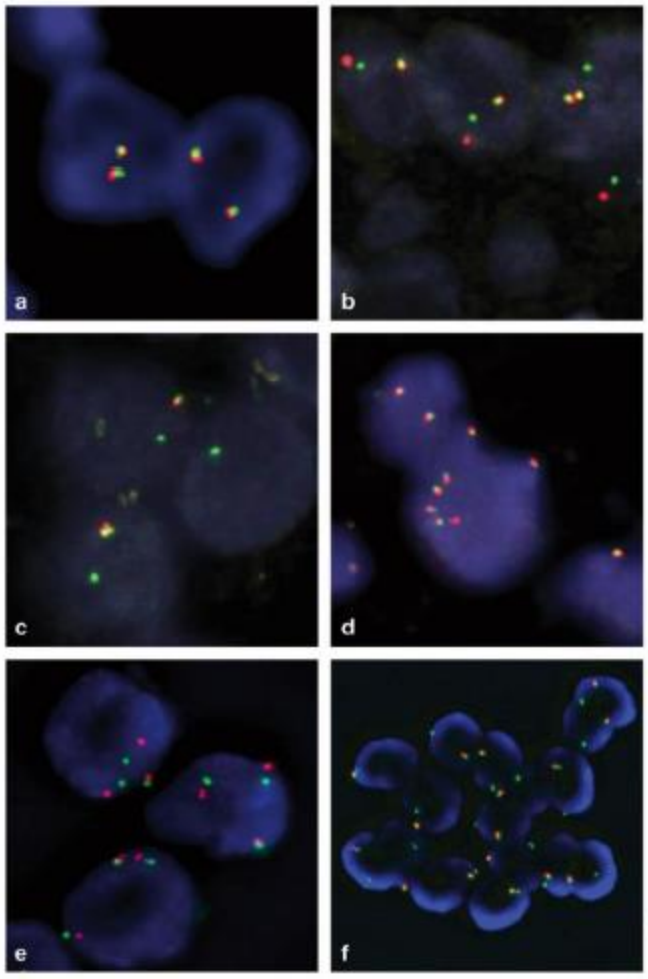
ROS1

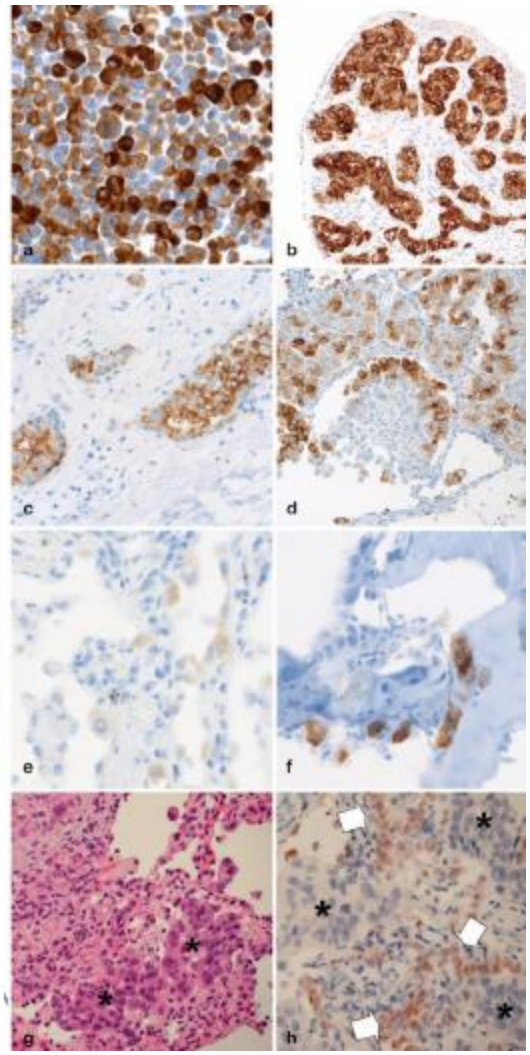
ROS1 Testing: Standard by FISH





Bubendorf L et al
Virchow Arch 2016, in press

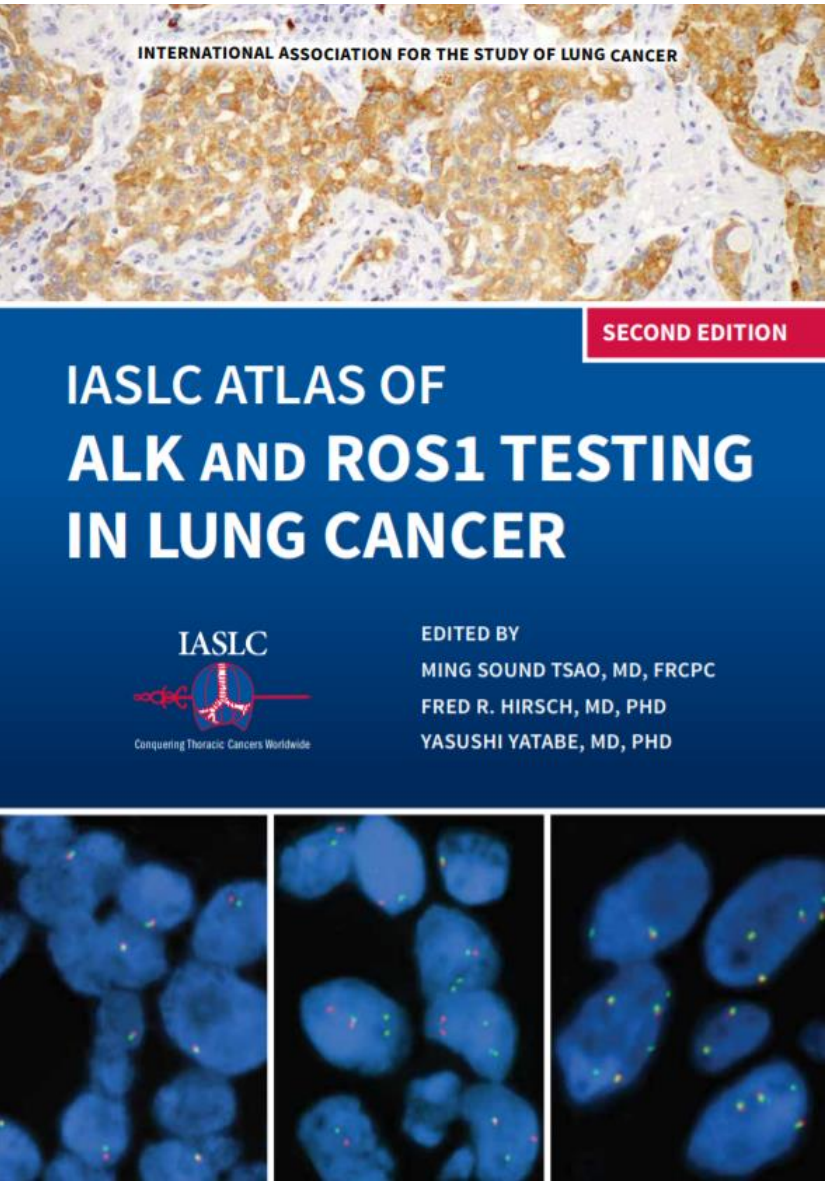




D4D6 antibody

Tsao MS in ELCC2018

ROS1

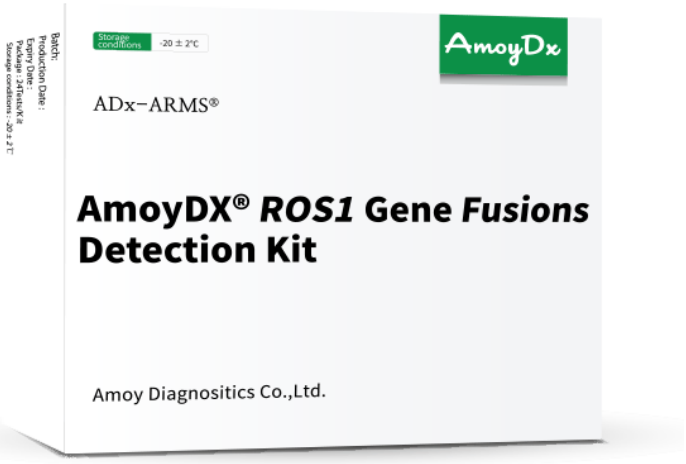


AmoyDx ROS1 Gene Fusions Detection Kit was Approved by South Korea MFDS as Companion Diagnostics for Pfizer's Crizotinib

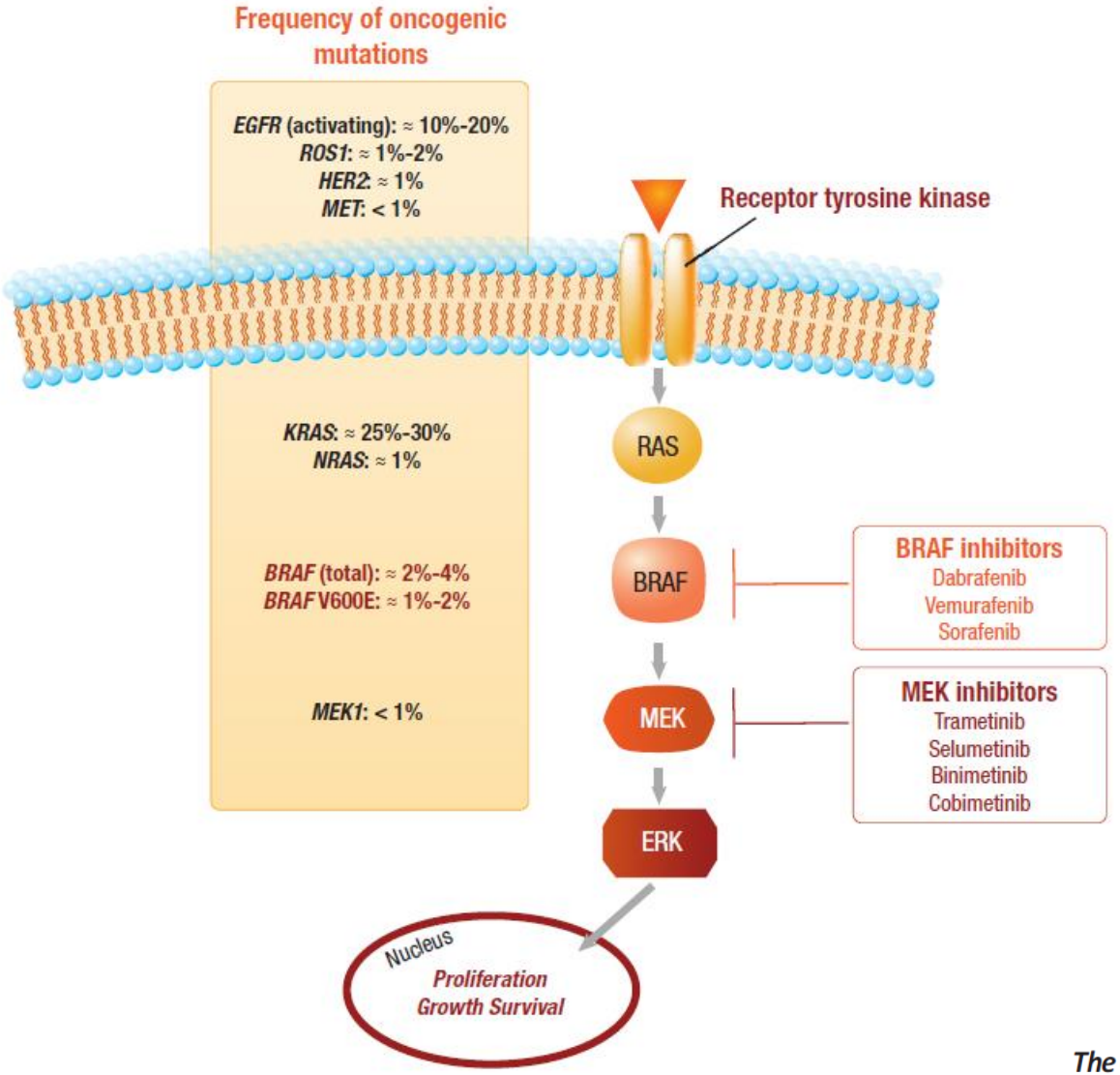
Published: Oct 01, 2018

October 1, 2018–Amoy Diagnostics of Xiamen, China today announced that it has received regulatory approval from South Korea's Ministry of Food and Drug Safety (MFDS) for its ROS1 fusion PCR assay as a companion diagnostics for Pfizer's ROS1 inhibitor Xalkori (Crizotinib).

Phase II Study of Crizotinib in East Asian Patients with ROS1-Positive Advanced NSCLC
*ORR = 71.7% (95% CI, 63.0% to 79.3%)
*Median PFS = 15.9 months



BRAF mutations in the context of mitogen-activated protein kinase (MAPK)



The Oncologist 2017;22:786–796

Comparison of available tests for BRAF mutations

	THxID™-BRAF Kit[1,2]	cobas® 4800 BRAF V600 Mutation Test[3-5]	Sanger sequencing[3]	HRM Analysis[3]	Pyro-sequencing[3]	NGS[3]	IHC[3]
Sensitivity	96.3% for V600E and 92.2% for V600K	97.3% for V600E and 62.9% for V600K	98%	98%	> 98%	98.6%	97%-100%
Specificity	100%	98.3%	100%	100%	90%	100%	98%
Limit of detection	5% for V600E and V600K	5%-7% for V600E; 35% for V600K	6.6%	6.6%	5%	2%	5%
Mutations detected	Approved for V600E and V600K	Approved for V600E only	99% of all mutations detectable	99% of all mutations detectable	Optimized for V600E	Multiplex detection of mutations	Antibody specific for V600E
Costs[a]	Medium	Medium	Medium	Low	High	Very high	Low

1. Marchant J, et al. *BMC Cancer.* 2014;14(519):1-9; 2. THxID™-BRAF [package insert]. Marcy-l'Etoile, France: bioMérieux; 2013; 3. Ihle MA, et al. *BMC Cancer.* 2014;14(13):1-13; 4. cobas® 4800 BRAF V600 Mutation Test [package insert]. Branchburg, NJ: Roche Molecular Systems; 2011; 5. Qu K, et al. *J Mol Diag.* 2013;15(6):790-795.

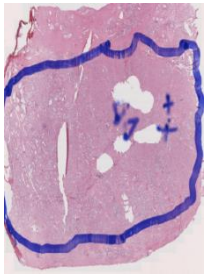
MSK-IMPACT: Integrated Mutation Profiling of Actionable Cancer Targets

Testing initiated 2014

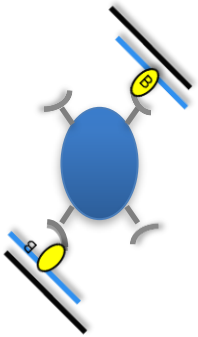
Versions

341 genes: 2014-15
410 genes: 2015-16
468 genes: 2016-18

DNA from **FFPE Tumor** and **Normal** cells



Capture DNA for **468 cancer genes**



Next-gen Sequencing (500 - 1000 x)

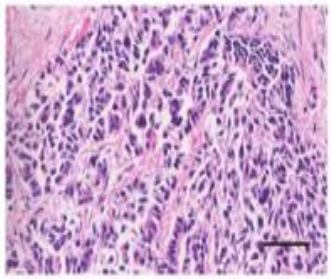
Align to genome and analyze

Somatic Mutations (Tumor-Normal Pairs):
Base Substitutions
Small Indels
Copy Number Alterations
Select Rearrangements

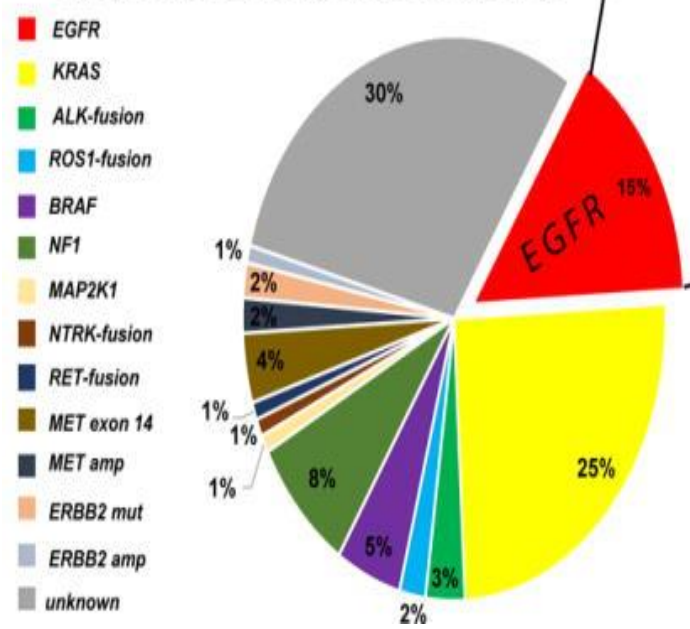
Cheng DT, *et al.*, *J Mol Diagnostics*, March 2015 - **Methodology**

A new way of looking at the lung ca oncogene pie chart…

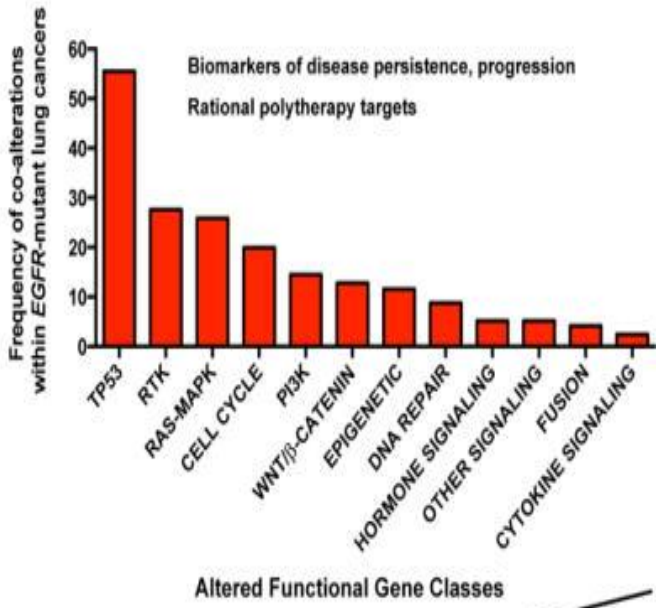
a Histologic classification of lung cancer



b Current single-gene driver oncogene classification of lung adenocarcinomas



c New model of co-occurring genetic alterations within *EGFR*-mutant lung cancers

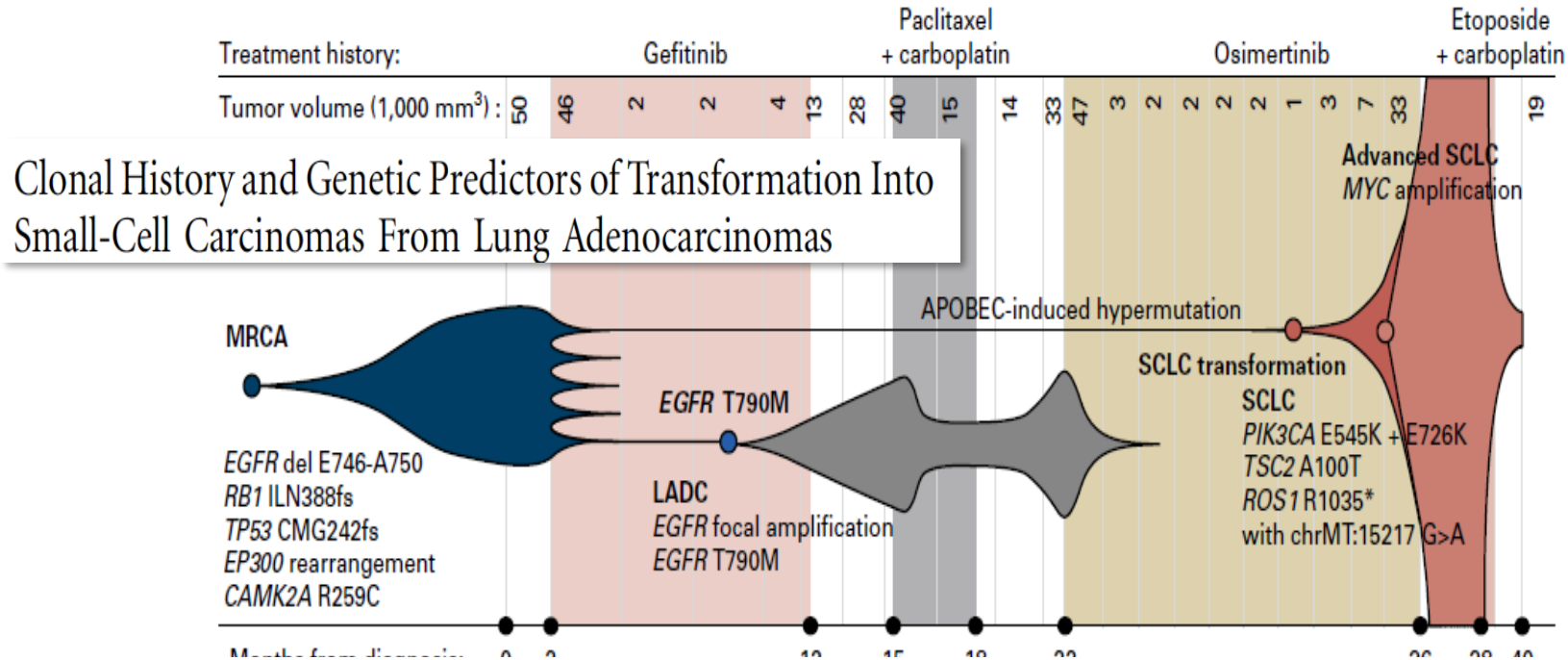


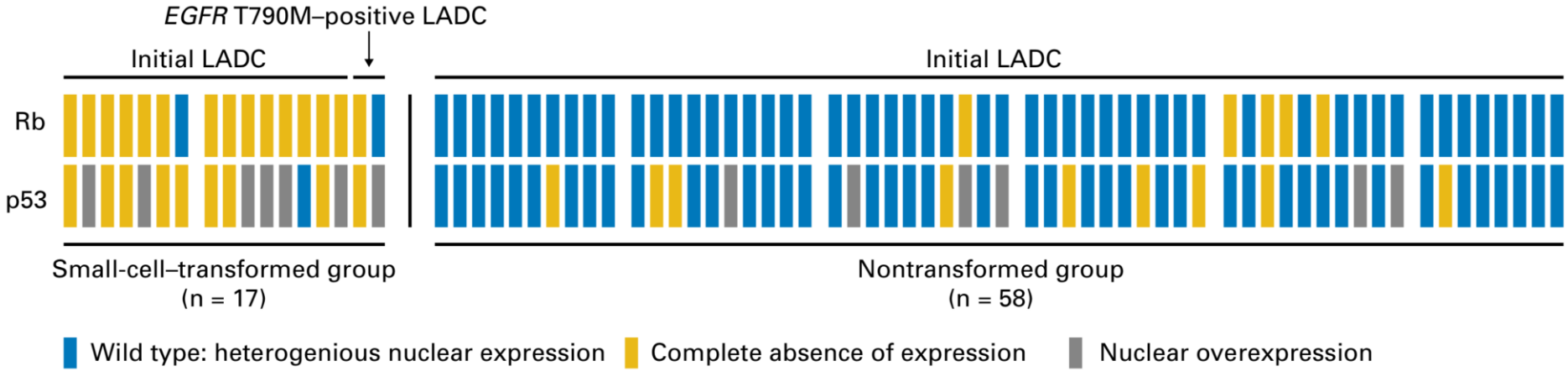
Evolution and clinical impact of co-occurring genetic alterations in advanced-stage *EGFR*-mutant lung cancers

Blakely C. et al

NATURE GENETICS VOLUME 49 | NUMBER 12 | DECEMBER 2017

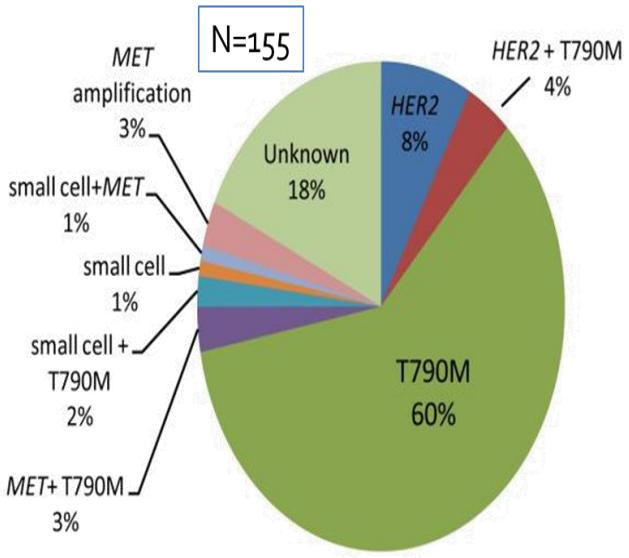
Rare Concurrent *TP53+RB1* Mutations pre-TKI also Predispose to Worse Outcomes





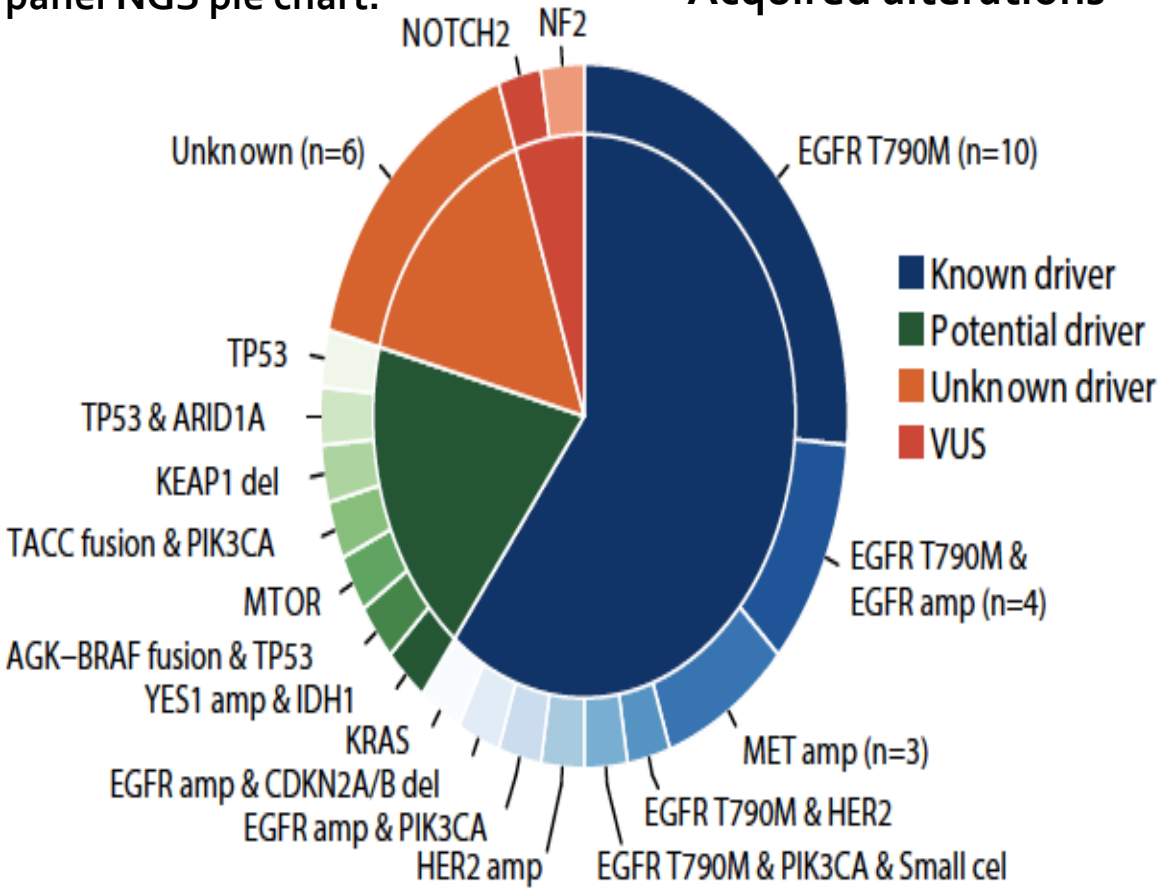
38 Paired samples (pre-post EGFR TKI): large panel NGS reveals richer landscape of AR mechanisms

Pre-NGS pie chart → **Large panel NGS pie chart:** **Acquired alterations**



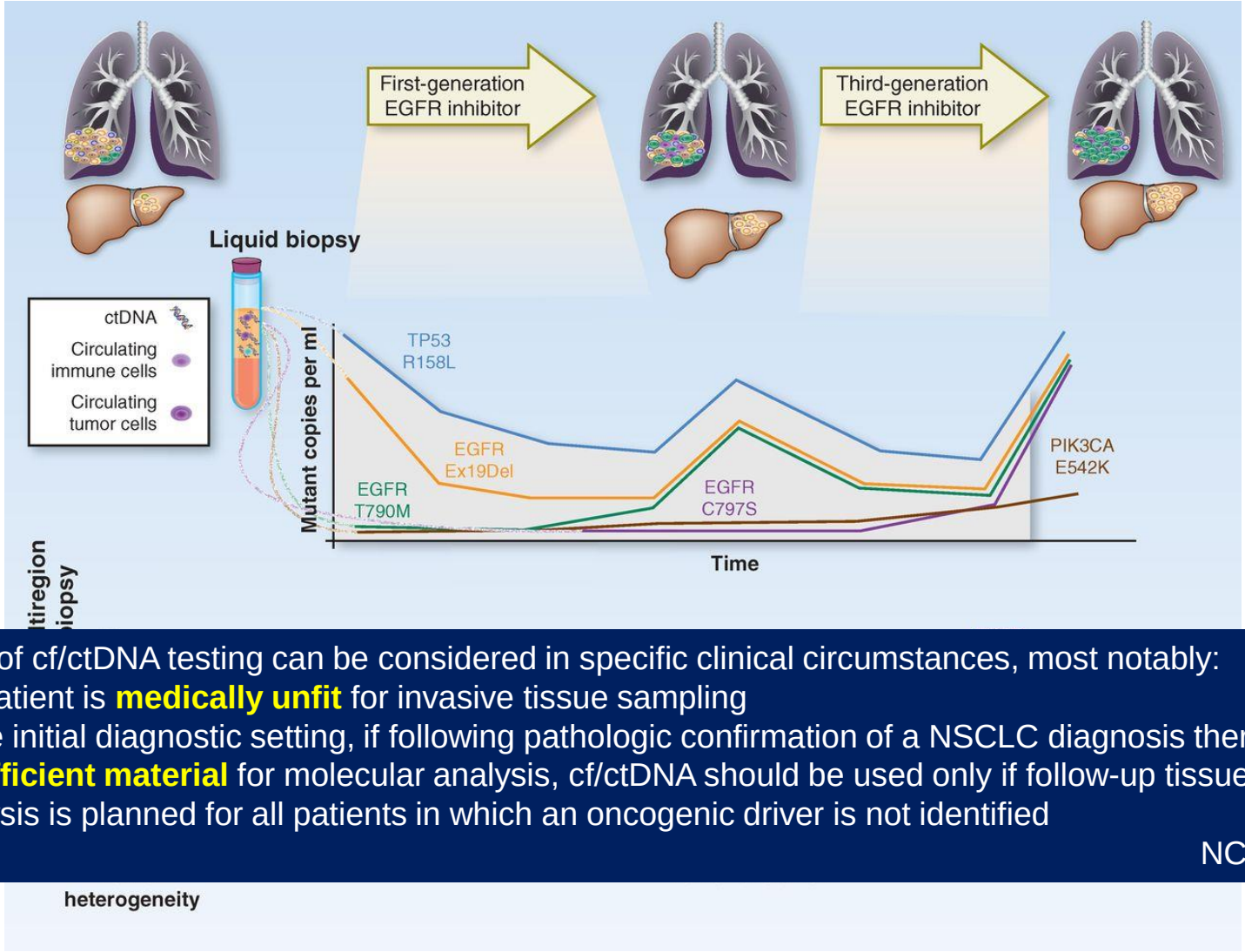
Analysis of Tumor Specimens at the Time of Acquired Resistance to EGFR-TKI Therapy in 155 Patients with *EGFR*-Mutant Lung Cancers

Clinical Cancer Res March 2013



Helena Yu et al. CCR Mar 2018

Diagnostic approaches to measure the impact of cancer therapies on clonal evolution



The use of cf/ctDNA testing can be considered in specific clinical circumstances, most notably:

- If a patient is **medically unfit** for invasive tissue sampling
- In the initial diagnostic setting, if following pathologic confirmation of a NSCLC diagnosis there is **insufficient material** for molecular analysis, cf/ctDNA should be used only if follow-up tissue-based analysis is planned for all patients in which an oncogenic driver is not identified

NCCN 2019

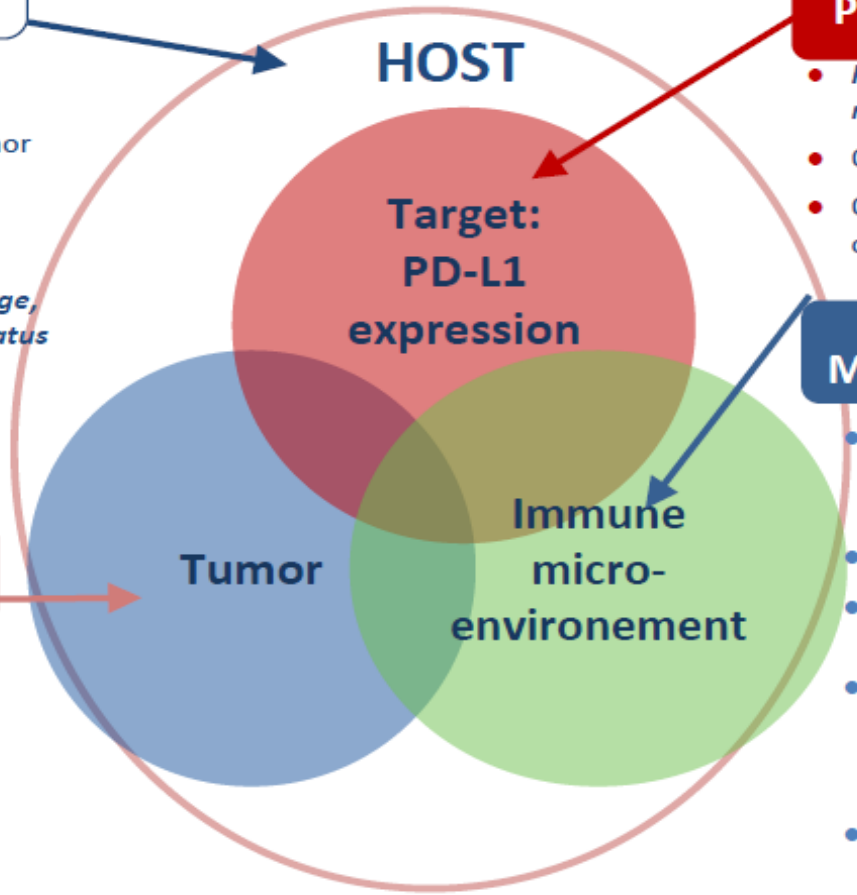
Cancer Discov 2017;7(8): 805–17

Host Characteristics and Environment

- Biomarkers which characterize the host environment, beyond tumor microenvironment, may predict response to IO treatment
- ***Clinical factors: gender, age, PS, histology, smoking status***
- ***Microbiome, Germline Genetics***

Tumor Antigens

- Biomarkers indicative of hypermutation & neo-antigens may predict response to IO treatment
- ***EGFR, KRAS, LKB1, p53 mutations, ALK+***
- ***TMB, MSI-High, Neo-Antigens, clonality***



PD-L1 expression

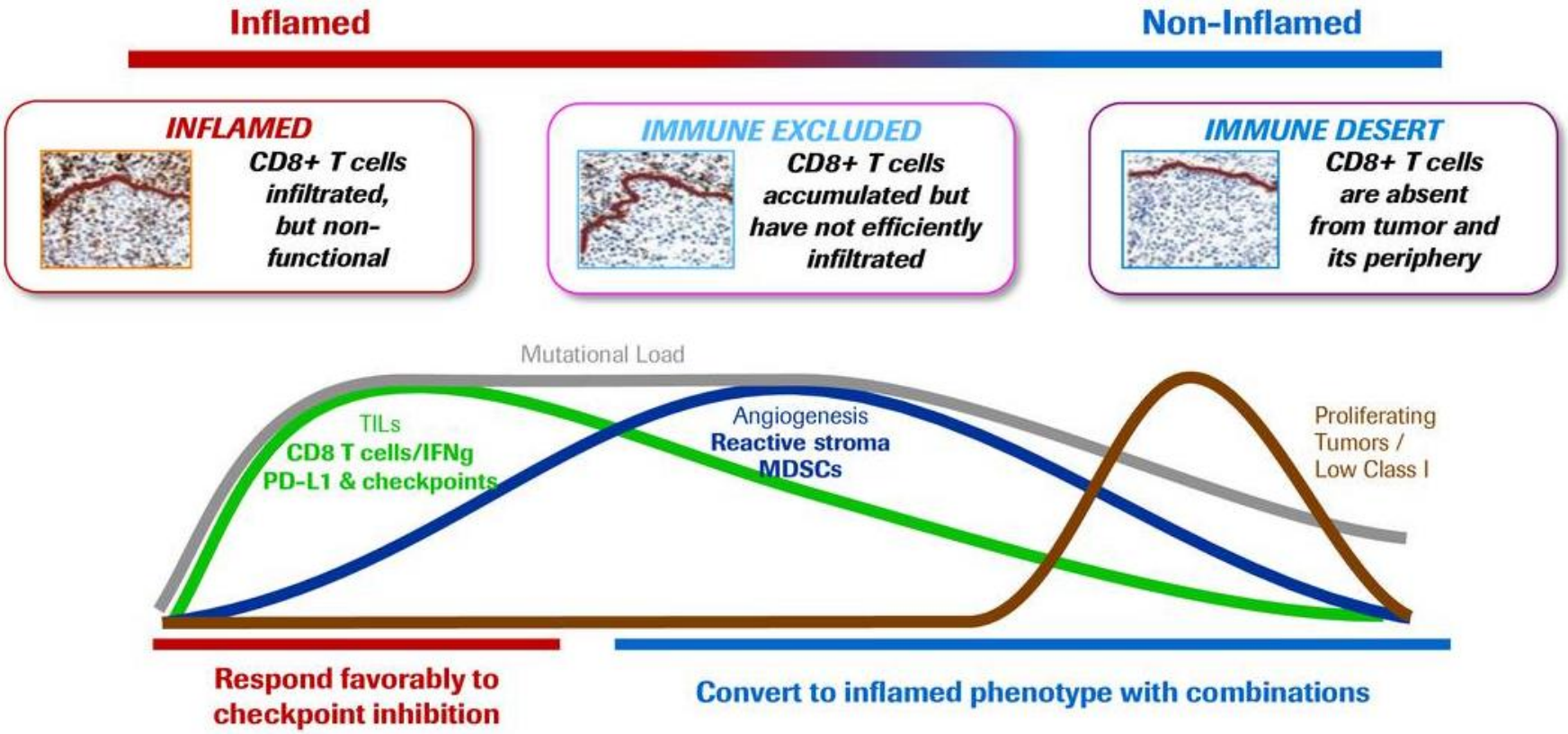
- ***IHC, gene expression, mRNA***
- On tumor cells
- On immune infiltrating cells

Tumor Immune Microenvironment

- Biomarkers that identify tumor immune system evasion beyond PD-1/CTLA-4
- ***Tregs, MDSCs, IDO, LAG3, …***
- Inflamed tumor, immune desert, immune excluded **phenotypes**
- Biomarkers (intra- or peri-tumoral) indicative of an inflamed phenotype may predict response to IO treatment
- ***CD8+T cell infiltration and functionality***
- ***TCR clonality***
- ***Immune gene signatures***

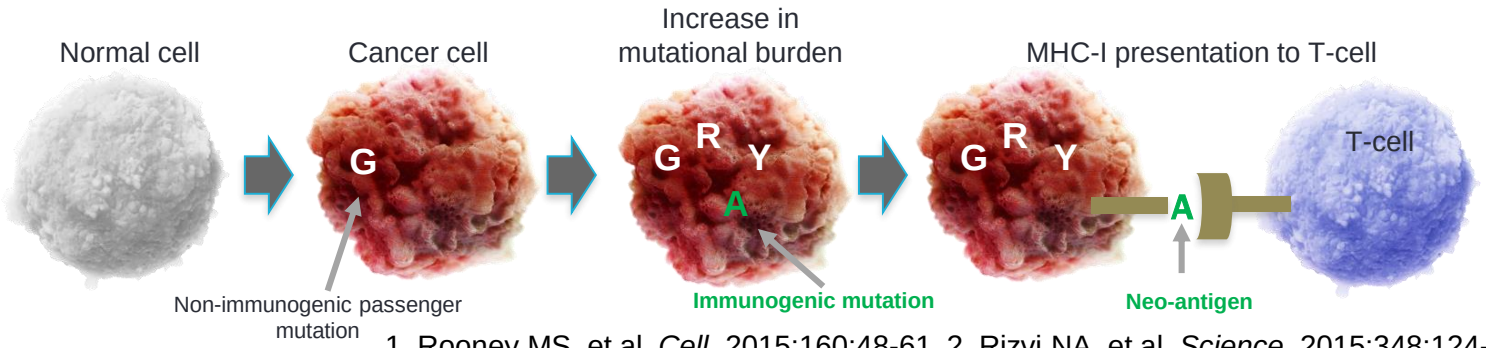
Modified from Peters, AACR 2017; Topalian, Nat Rev Cancer 2016

Tumour immune phenotypes provide a framework for understanding CIT resistance mechanisms

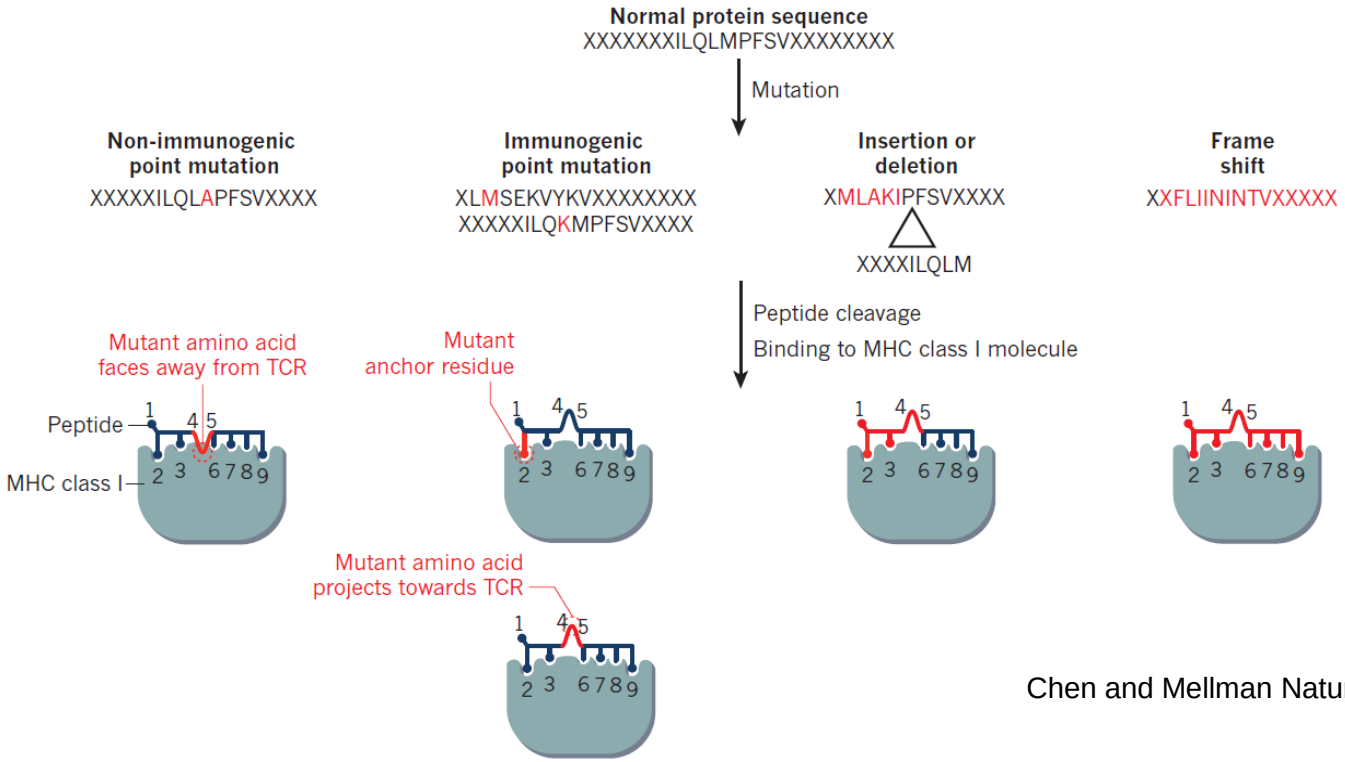


Modified from Hegde et al. Clin Canc Res 2016

TMB as a predictor of clinical benefit to PD-L1/PD-1 inhibitors



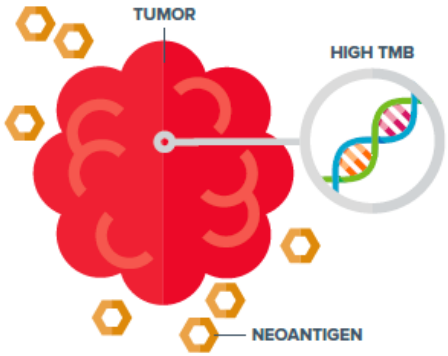
1. Rooney MS, et al. *Cell.* 2015;160:48-61. 2. Rizvi NA, et al. *Science.* 2015;348:124-128.



Chen and Mellman Nature (2017) 541: 321

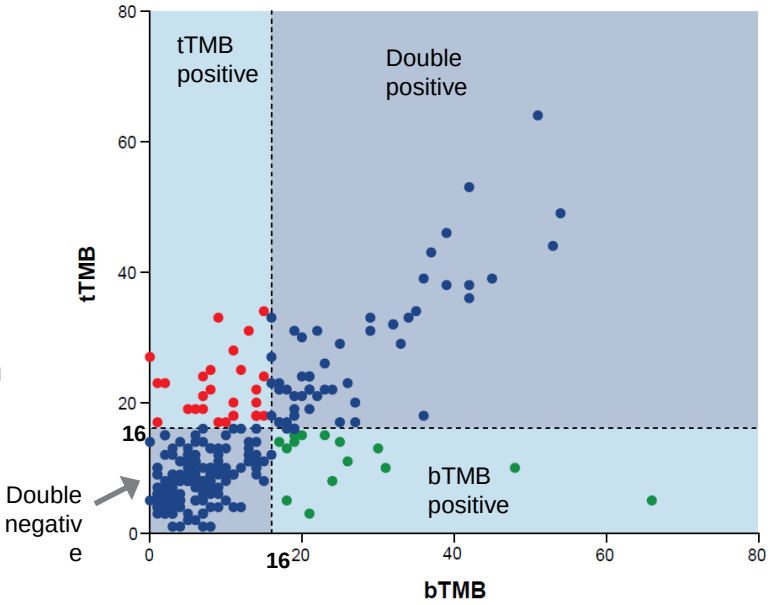
Tumour mutational burden (TMB): An emerging biomarker in NSCLC

Tumour mutational burden (TMB) is the
TOTAL NUMBER OF MUTATIONS
per coding area of a tumour genome



Higher TMB levels are correlated with
HIGHER LEVELS OF NEO-ANTIGENS
which help our immune system to recognise tumours1,2

TMB can be assessed in both
BLOOD AND TISSUE



Blood-based TMB (bTMB) correlates with tissue-based TMB (tTMB) in clinical samples[3,4]

1. Brown et al. Genome Res. 2014;24:743-750.
2. Schumacher & Schreiber. Science. 2015;348(6230):69-74.
3. Gandara DR, et al. *Ann Oncol*. 2017;28(suppl_5):v460-496.
4. Gandara DR, et al. *Nature Med*. 2018;Published online.

F1CDx

FOUNDATION MEDICINE®

MSK-Impact

Memorial Sloan Kettering Cancer Center

Oncomine TML

ThermoFisher SCIENTIFIC

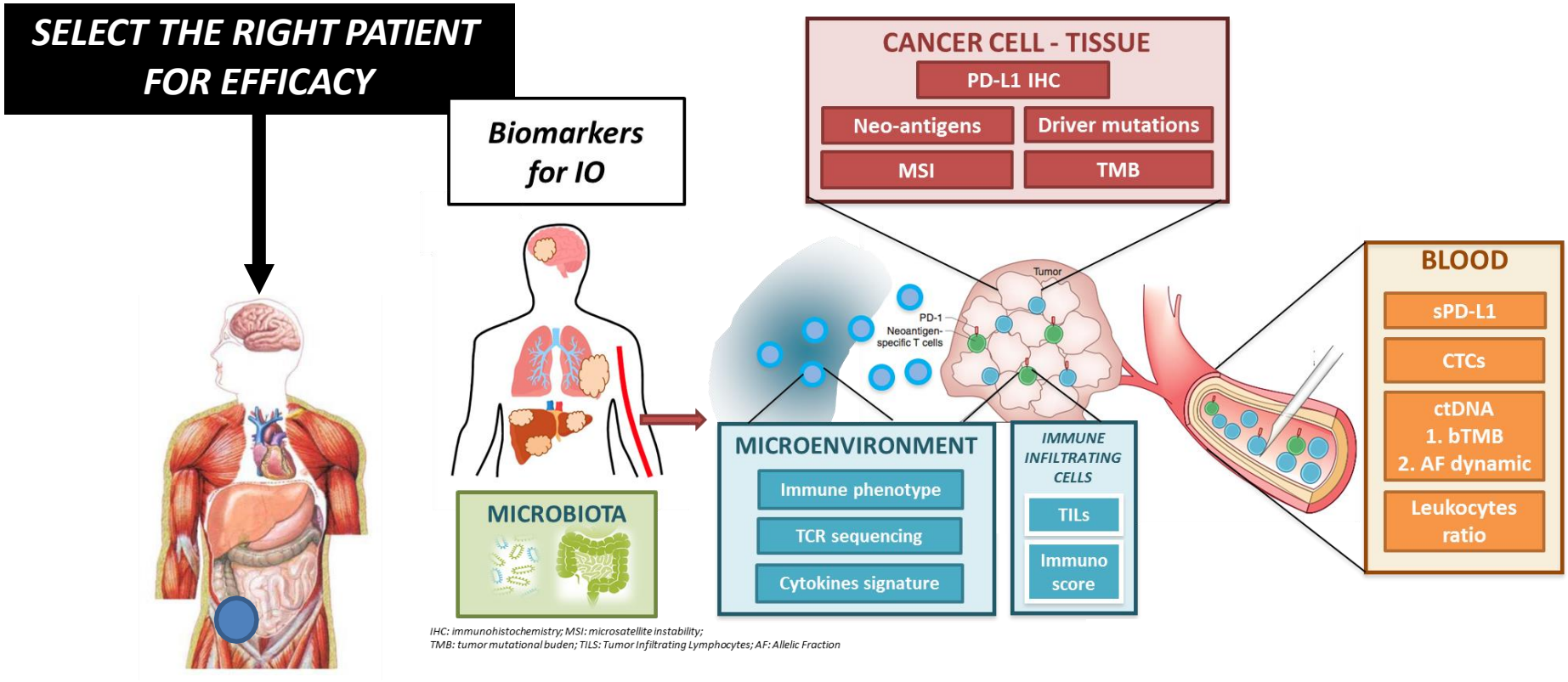
• FDA cleared	+
• Actionable mutations	+
• Outsource service	-
• High DNA input	-

• RUO/LDT	-
• Separate test	-
• In house	+
• DNA input 20ng	+

Good correlation with WES

Lukas Bubendorf, University Hospital Basel, Switzerland

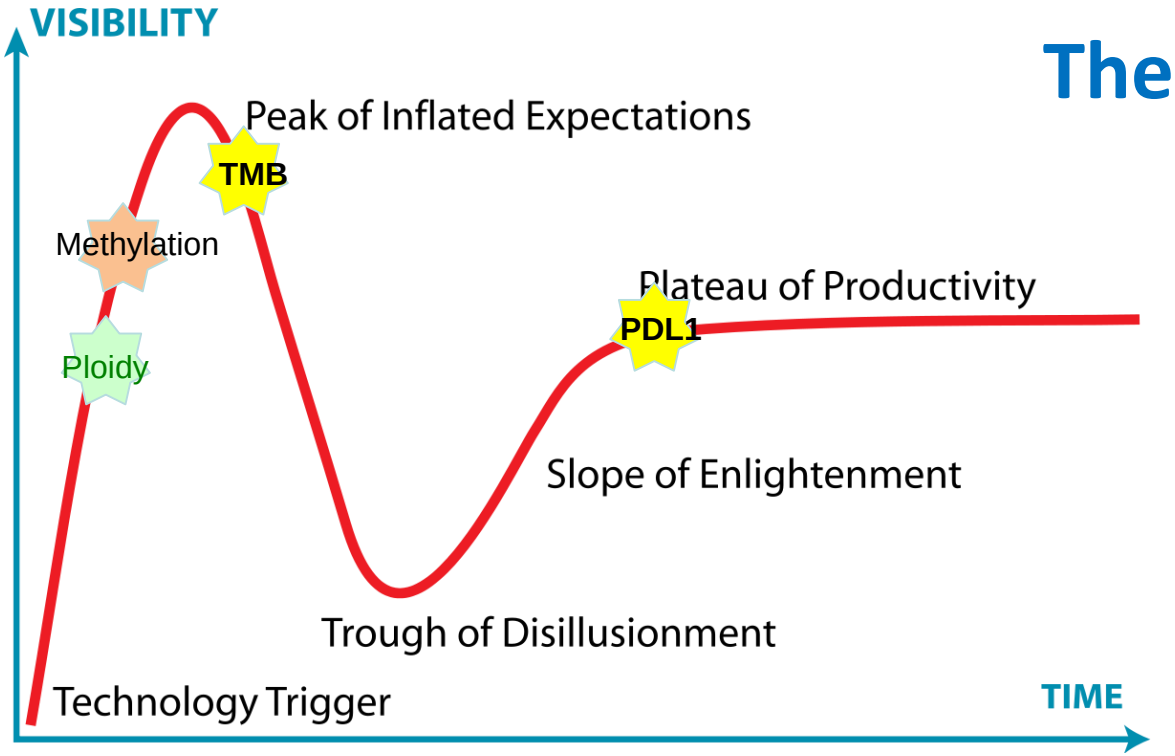
Whom to Give IO?



Adaptation courtesy of A. Marabelle

Ferrara R, et al. *J Thorac Oncol.* 2017;11(Suppl 2): Abstract MA10.11. Saâda-Bouzid E, et al. *Ann Oncol.* 2017;28(7):1605-1611. Champiat S, et al. *Clin Cancer Res.* 2017;23(8):1920-1928.

The hype cycle



Gartner;
https://en.wikipedia.org/wiki/Hype_cycle

Predictive biomarkers of IO

- Consensus for translational research -

Priority	Issues
High	Diagnostic reliability of PD-L1 tests on cytological samples and small biopsies
	PD-L1 levels on liquid biopsy
	Biomarkers of tumor foreignness
	Mechanisms of resistance in PD-L1 positive tumors
	Mechanisms of responsiveness in PD-L1 negative tumors
Moderate	Development of common strategies to detect at the RNA level gene fusion (ALK, ROS1, RET) and immune signature biomarkers
	Archival versus rebiopsy specimens for PD-L1 expression
	Heterogeneity of PD-L1 expression in primary versus metastatic sites
Low	Influence of prior treatments on PD-L1 expression
	Evaluation of the role of PD-L1 expression in NSCLC vs. other solid tumors
	Correlation between PD-L1 expression and other driver mutations

Results from an Experts Panel Meeting of the Italian Association of Thoracic Oncology

Transl Lung Cancer Res 2017;6(3):373-386

Annals of Oncology 30: 171–210, 2019
doi:10.1093/annonc/mdy554
Published online 28 December 2018

SPECIAL ARTICLE

Pan-Asian adapted Clinical Practice Guidelines for the management of patients with metastatic non-small-cell lung cancer: a CSCO–ESMO initiative endorsed by JSMO, KSMO, MOS, SSO and TOS

Y.-L. Wu[1*], D. Planchard[2], S. Lu[3], H. Sun[4], N. Yamamoto[5], D.-W. Kim[6], D. S. W. Tan[7], J. C.-H. Yang[8], M. Azrif[9], T. Mitsudomi[10], K. Park[11], R. A. Soo[12], J. W. C. Chang[13], A. Alip[14], S. Peters[15] & J.-Y. Douillard[16]

Recommendation 2: pathology/molecular biology	
2a	Adequate tissue material for histological diagnosis and molecular testing should be obtained to allow for individual treatment decisions [A=100%]
2b	Pathological diagnosis should be made according to the 2015 WHO classification of lung tumours [A=100%]
2c	Specific subtyping of all NSCLCs is necessary for therapeutic decision making and should be carried out wherever possible. IHC stains should be used to reduce the NSCLC-NOS rate to fewer than 10% of cases diagnosed [A=100% and 1V, A]
2d	**EGFR** mutation status should be systematically analysed in advanced NSCC [A=100% and I, A]. Test methodology should have adequate coverage of mutations in exons 18–21, including those associated with resistance to some therapies [A=100% and III, B]. At a minimum, when resources or material are limited, the most common activating mutations (exon 19 deletion, exon 21 L858R point mutation) should be determined [A=100% and I, A]
2d-1	**The availability of a TKI effective against T790M-mutant recurrent disease makes T790M testing mandatory on the occurrence of first-/second-generation EGFR-TKI resistance** (added retrospectively)

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

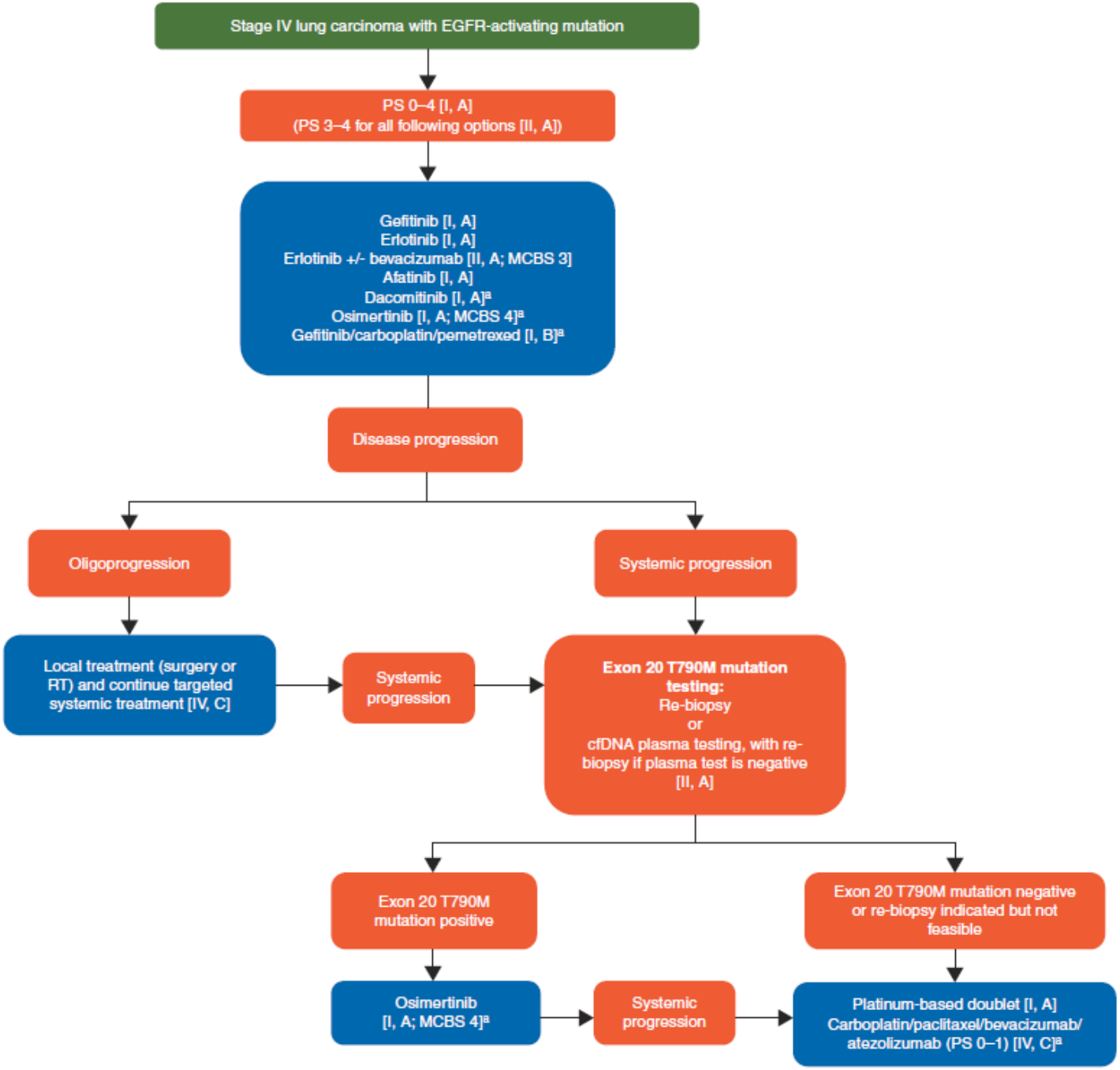
Annals of Oncology 30: 171–210, 2019
doi:10.1093/annonc/mdy554
Published online 28 December 2018

SPECIAL ARTICLE

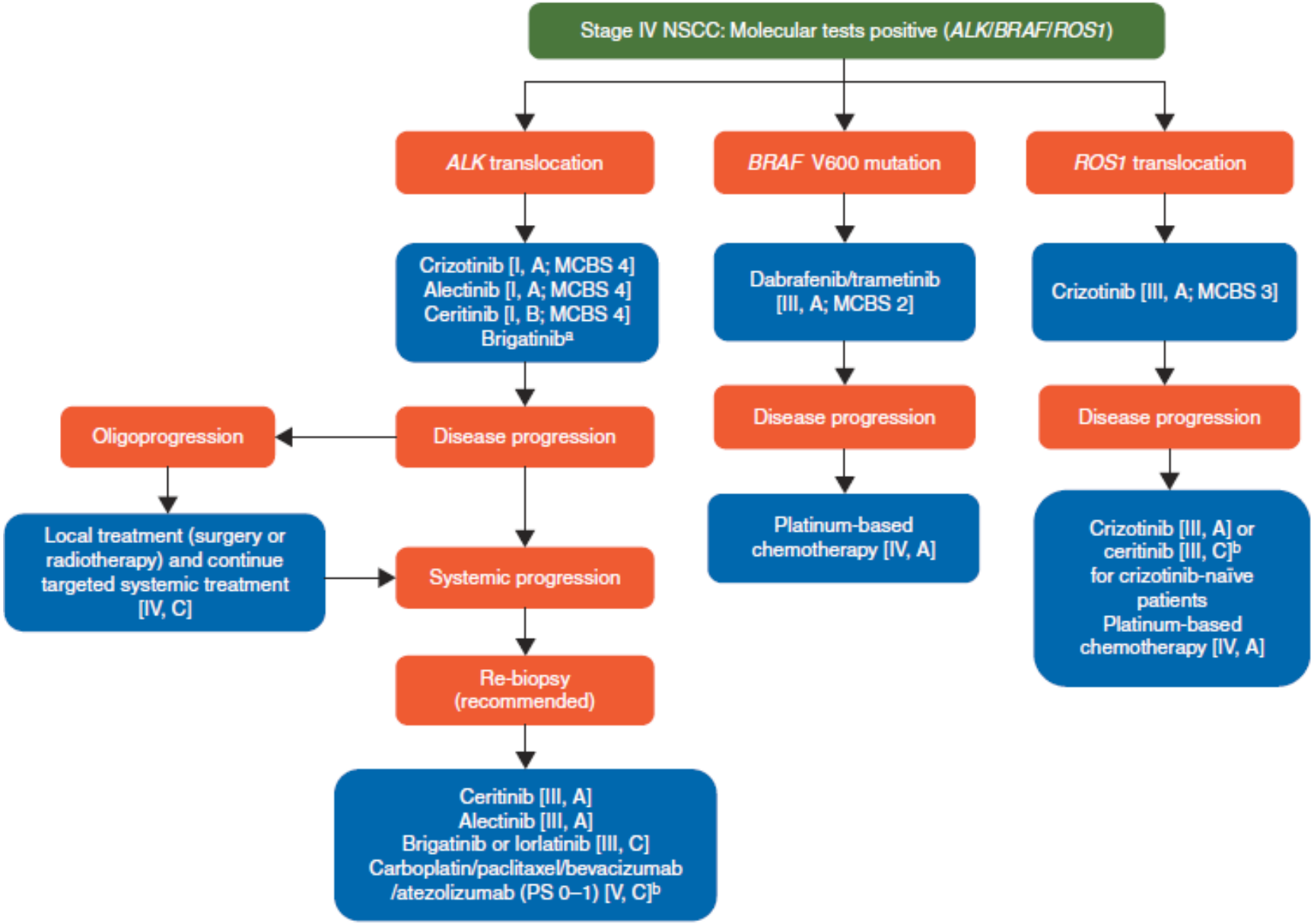
Pan-Asian adapted Clinical Practice Guidelines for the management of patients with metastatic non-small-cell lung cancer: a CSCO–ESMO initiative endorsed by JSMO, KSMO, MOS, SSO and TOS

Recommendation 2: pathology/molecular biology	
2e	Testing for ALK rearrangement should be systematically carried out in advanced NSCC [A=100% and I, A]
2f	Detection of the ALK translocation by **FISH** remains a standard, but **IHC** with high-performance ALK antibodies and validated assays may be used for screening [A=100% and III, A] and have recently been accepted as an equivalent alternative to FISH for ALK testing
2g	Testing for ROS1 rearrangement should be systematically carried out in advanced NSCC [A¼100% and II, A]. Detection of the ROS1 translocation by **FISH** remains a standard. **A validated RT-PCR test may be used as an alternative**. IHC may be used as a screening approach [A=100% and IV, A]
2h	BRAF V600 mutation status should be systematically analysed in advanced NSCC for the prescription of BRAF/MEK inhibitors [A=100% and II, A]
2i	Molecular EGFR and ALK testing is not recommended in patients with a confident diagnosis of SCC, except in unusual cases, e.g. never/former light smokers or long-time ex-smoker [A=100% and IV, A]
2j	If available, multiplex platforms for molecular testing are preferable [A=100% and III, A]
2k	PD-L1 IHC should be systematically determined in advanced NSCLC. Testing is required for pembrolizumab therapy **in all lines of treatment** and may also be informative when nivolumab or atezolizumab are used **as monotherapy in the second-line setting** [A=100% and I, A]

Ann Oncol 2019;30(2):171-210



Ann Oncol 2019;30(2):171-210



Ann Oncol 2019;30(2):171-210

Earth Sees First Image Of A Black Hole

BY BILL CHAPPELL — APR, 10 2019