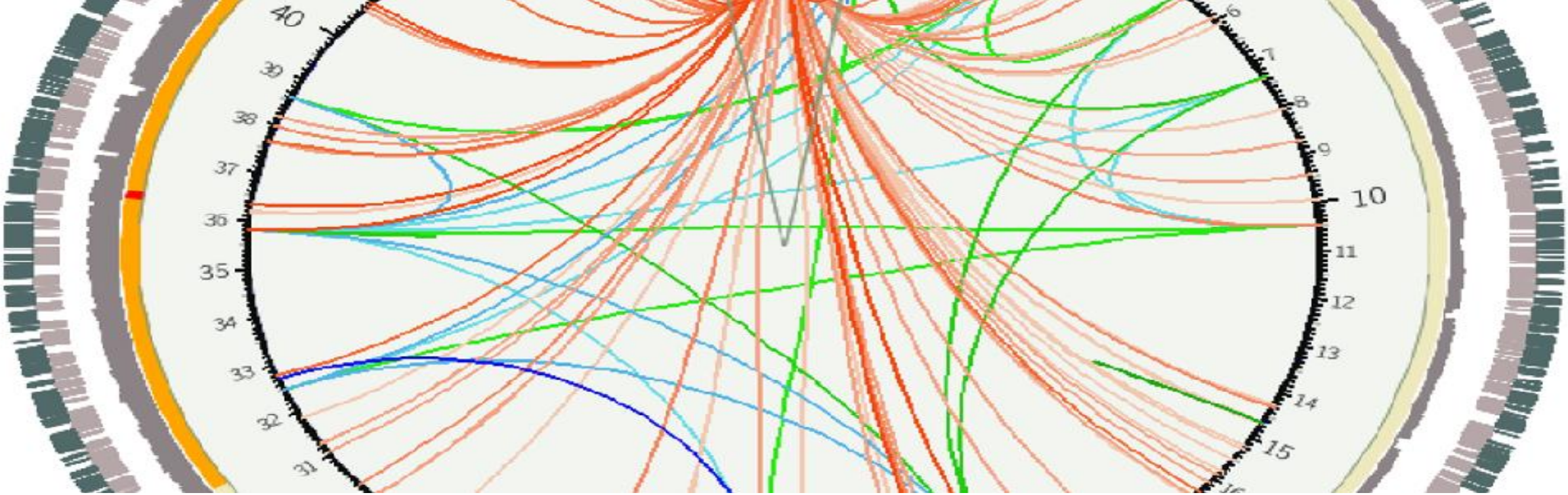


THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Estado Actual del Diagnóstico Molecular en Cáncer de Pulmón

XXIV Congress Sociedad Chilena de Anatomia Patologica (SCHAP)
November 11-13, 2020, Virtual Meeting, Santiago, Chile

Ignacio I. Wistuba, M.D
Division Head ad interim, Division of Pathology and Laboratory Medicine.
Professor and Chair, Department of Translational Molecular Pathology
Co-Director, Khalifa Institute for Personalized Cancer Therapy (IPCT)
The University of Texas MD Anderson Cancer Center, Houston, TX.

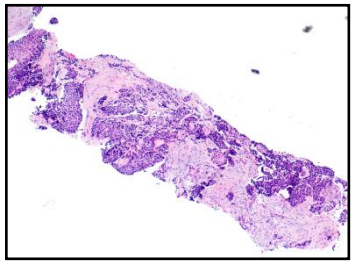
Disclosures

- **Advisory Board:** Genentech/Roche, Bayer, Bristol-Myers Squibb, Astra Zeneca/Medimmune, Pfizer, HTG Molecular, Asuragen, Merck, GlaxoSmithKline, Guardant Health, Oncocyte, Flame, and MSD.
- **Speaker**: Medscape, MSD, Genentech/Roche, Platform Health, Pfizer, AstraZeneca, Merck
- **Research support**: Genentech, Oncoplex, HTG Molecular, DepArray, Merck, Bristol-Myers Squibb, Medimmune, Adaptive, Adaptimmune, EMD Serono, Pfizer, Takeda, Amgen, Karus, Johnson & Johnson, Bayer, Iovance, 4D, Novartis, and Akoya.

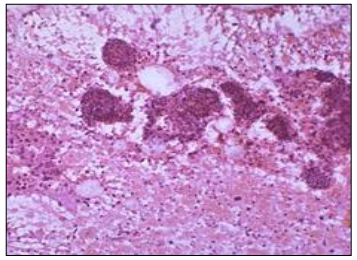
Paradigms in Lung Cancer Molecular Pathology - 2020

- Histology subtyping of lung cancer is clinically important
- Multiple clinically relevant molecular abnormalities ("driver alterations") have been detected and can be used to direct targeted therapy and improve patients' outcomes
- Liquid biopsy represents an alternative option for molecular testing, and potentially, early diagnosis
- Immunotherapy-related biomarkers are part of diagnosis: *PD-L1 IHC, microsatellite instability (MSI), and Tumor Mutational Burden (TMB)*
  - However, additional biomarkers are needed.

Diagnostic Algorithm for Lung Cancer Diagnosis 2020



Biopsy

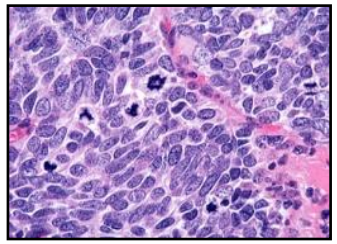


Cytology

Blood

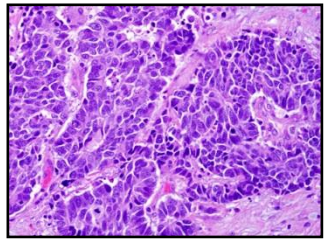
cfDNA Testing
(Liquid Biopsy)

SCLC



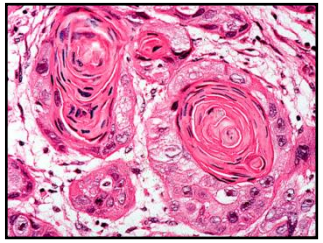
Morphology

LCNEC



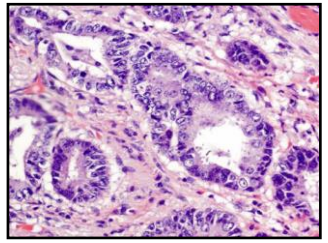
Morphology
IHC NE (+)

Squamous



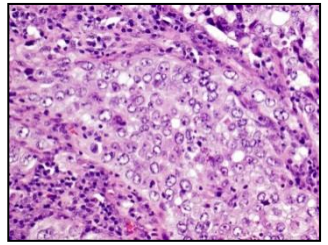
Morphology
IHC p63/p40 (+)

Adenoca



Morphology
IHC TTF1 (+)

NSCLC-NOS



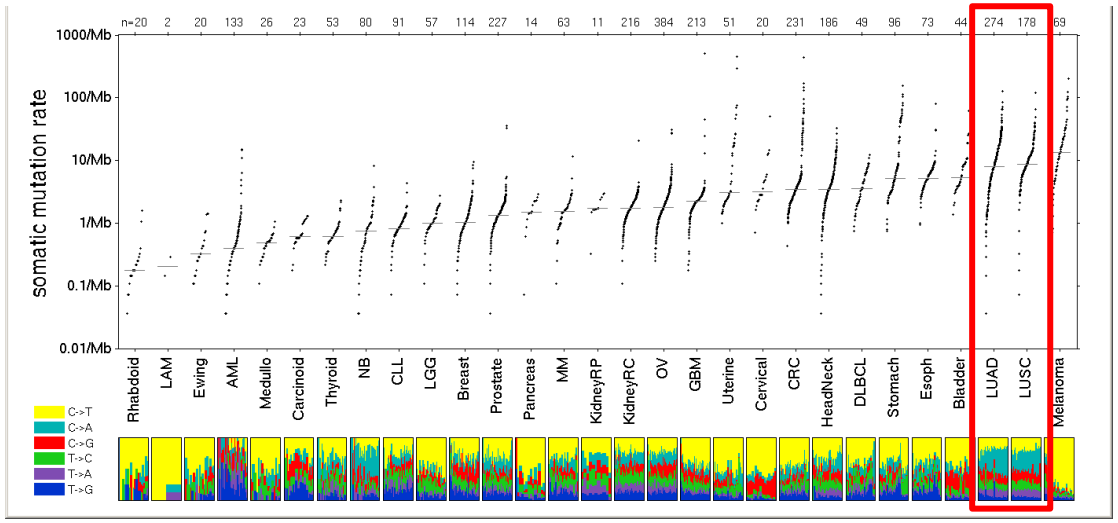
Morphology
IHC (-)

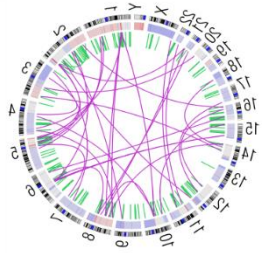
EGFR and *BRAF* mutation, *ALK*, *ROS1, RET* and *NTRK* fusions, *MET ex14* splicing

PD-L1 IHC

Cancer

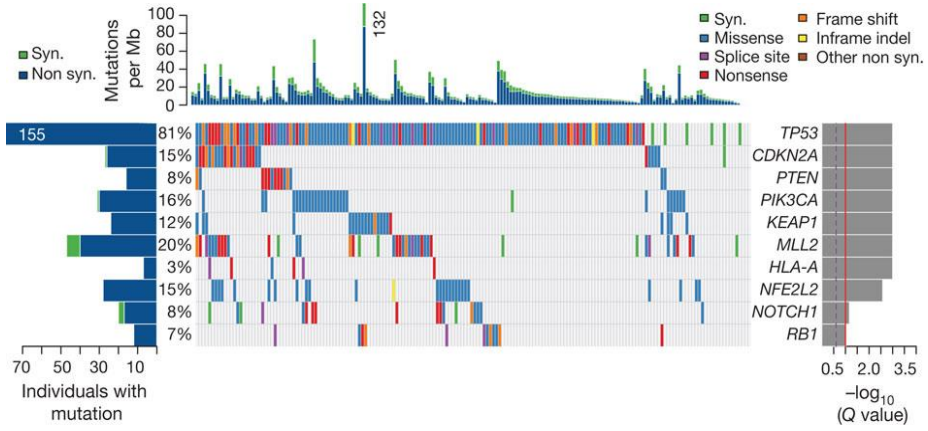
Non-Small Cell Lung Carcinomas (NSCLC) Show High Number of Somatic Mutations





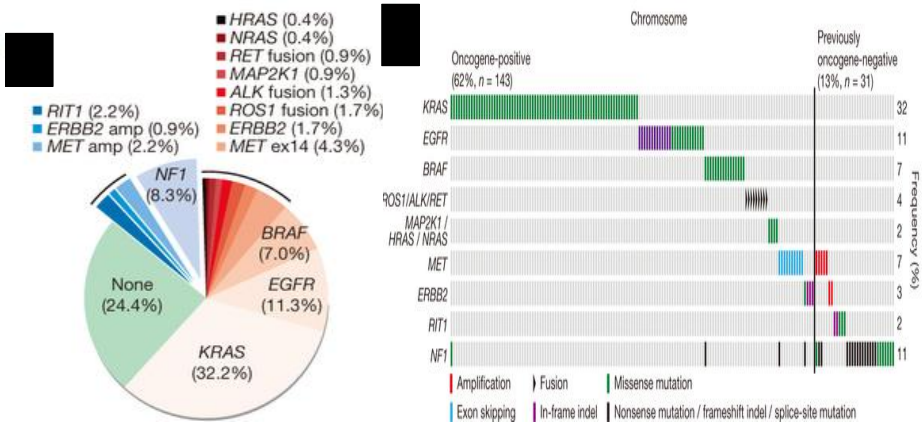
Lawrence et al., Nature, 2013

TCGA, Squamous Cell Carcinoma



PS Hammerman et al., (TCGA) Nature, 2012

TCGA, Adenocarcinoma

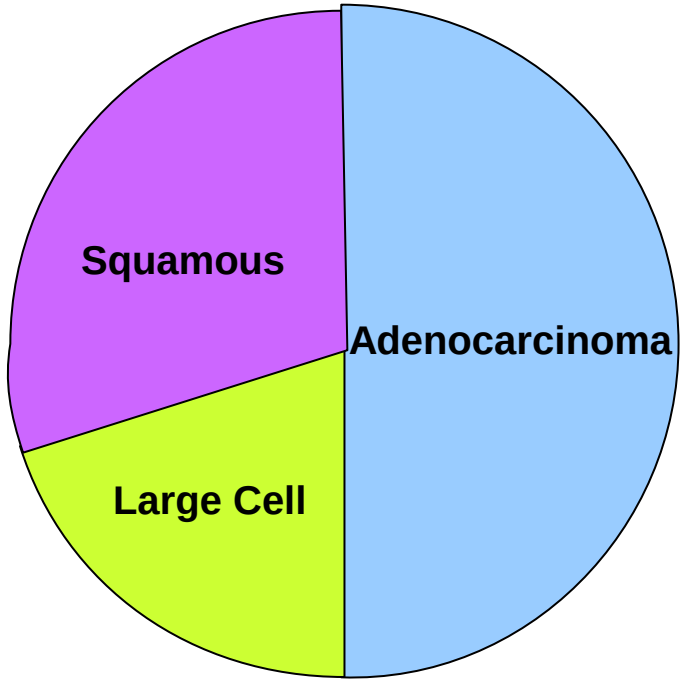


EA Collisson et al., (TCGA), Nature, 2014

Cancer

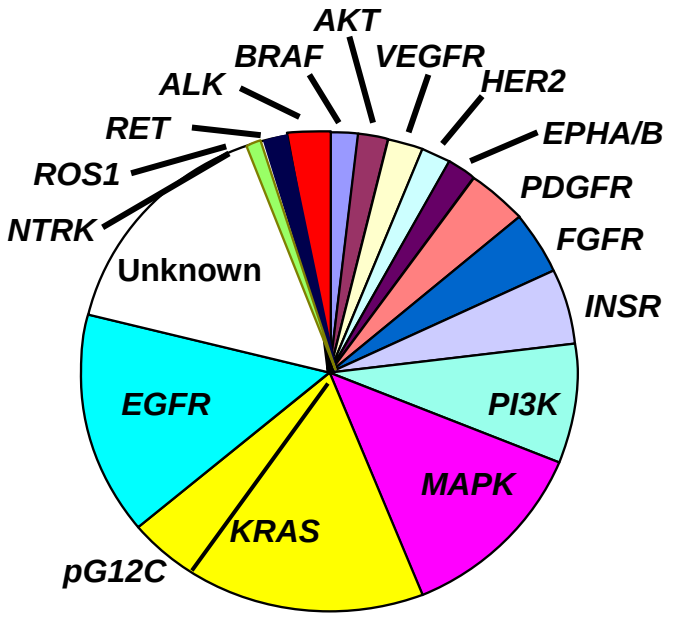
Molecular Testing for NSCLC - 2020

Traditional

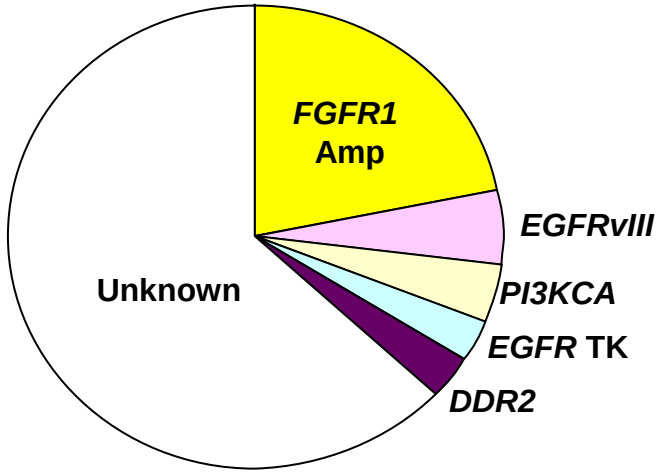


Adapted from W. Pao and N Girard, Lancet Oncol, 2011

Adenocarcinoma



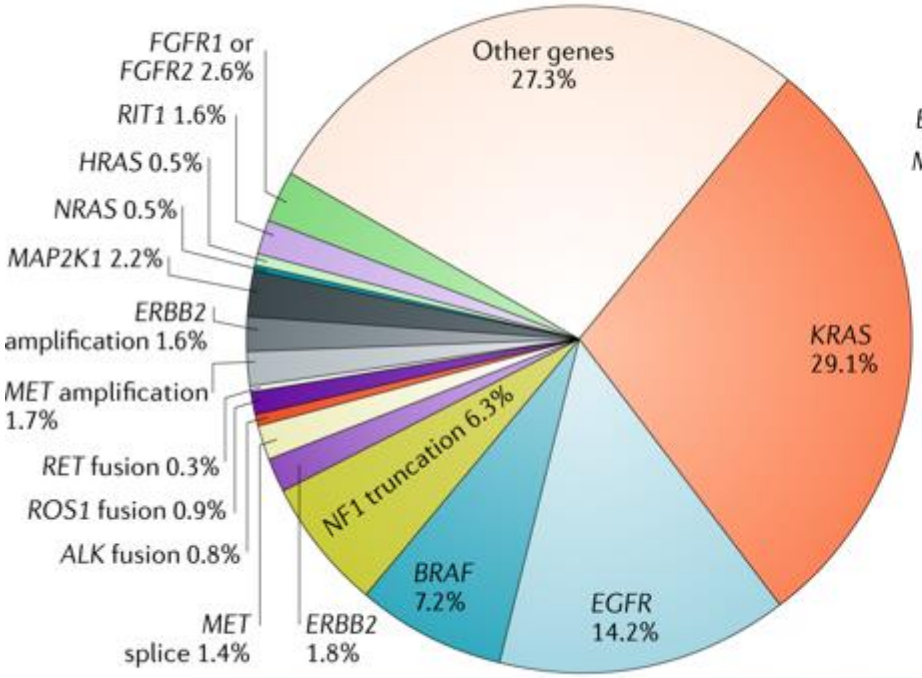
Squamous Cell Ca



Cancer

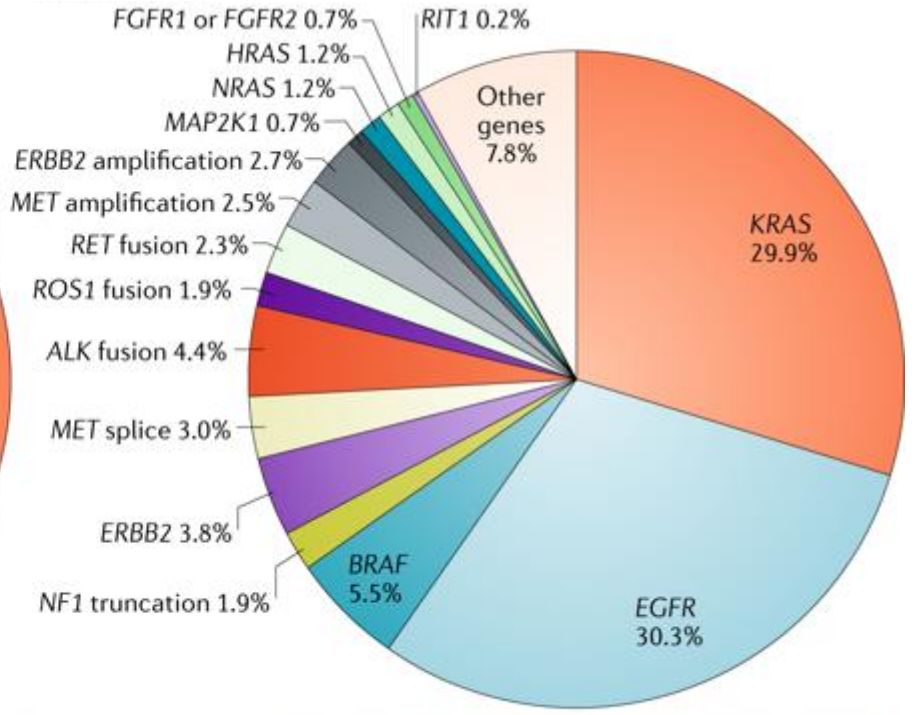
Genomic Abnormalities in Lung Adenocarcinoma

Early Stage



Data from TCGA (Sanchez-Vega et al.[178], Ellrott et al.[179] and Hoadley et al.[180]), Imielinski et al.[62] and Kadara et al.[133] (n = 741)

Metastatic Stage

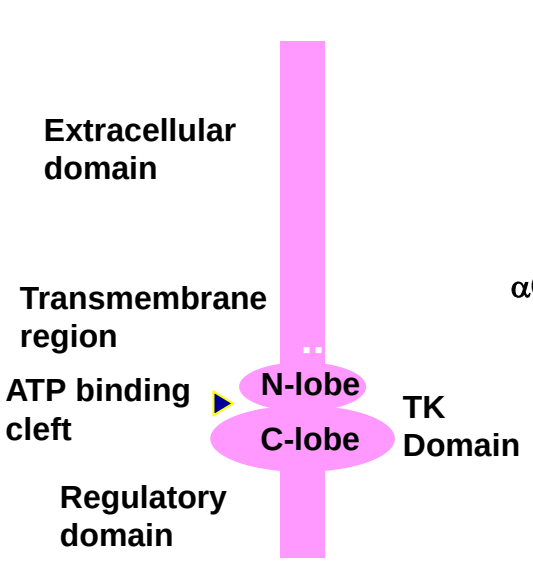


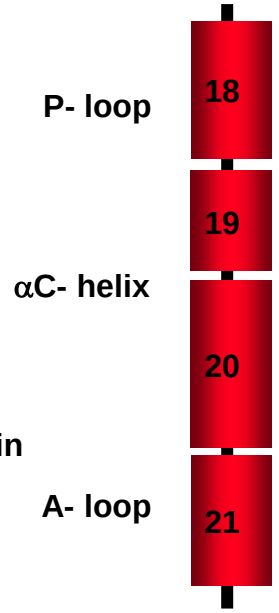
Data from MSK-IMPACT (Jordan et al.[59]) and FoundationOne (Frampton et al.[15]) panels (n = 5262)

Cancer Discovery

F. Skoulidis, Cancer Discovery, 2019

EGFR Mutations in Lung Adenocarcinoma





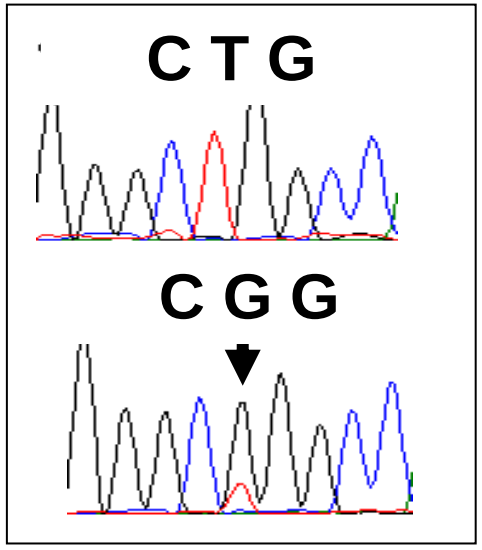
Deletions - 46%

Duplications Insertions - 9%

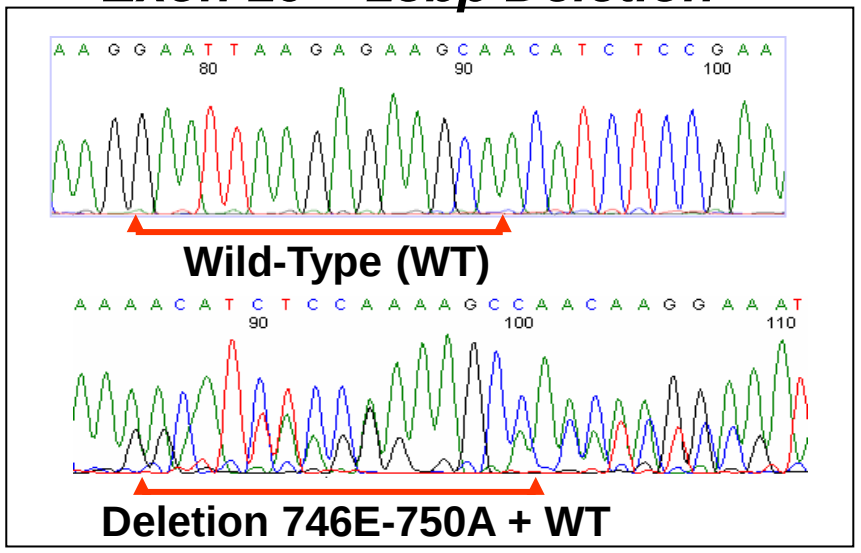
L858R - 39%

Exon 21 – L858R Mutation

***EGFR* Sequencing**

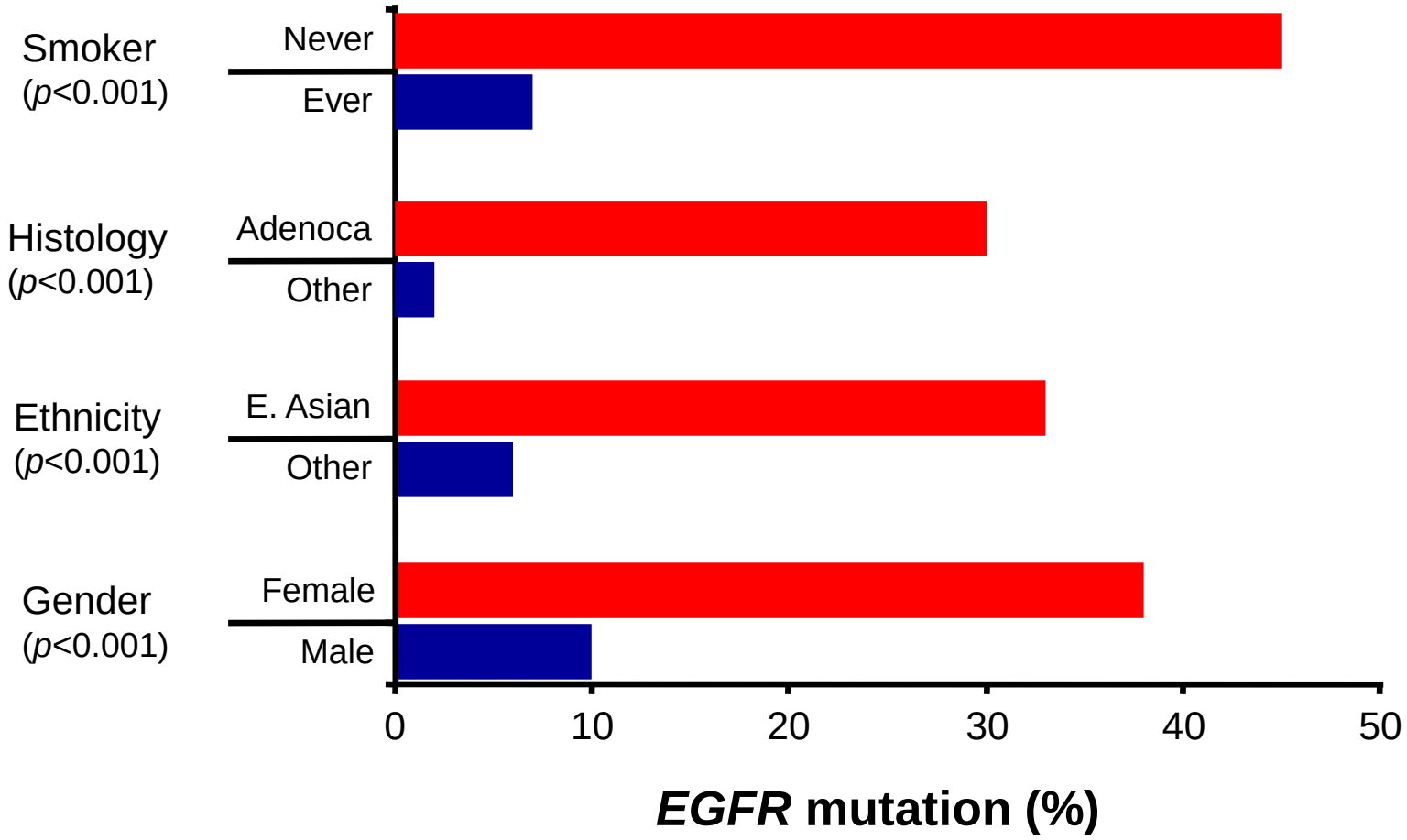


Exon 19 – 15bp Deletion



Cancer

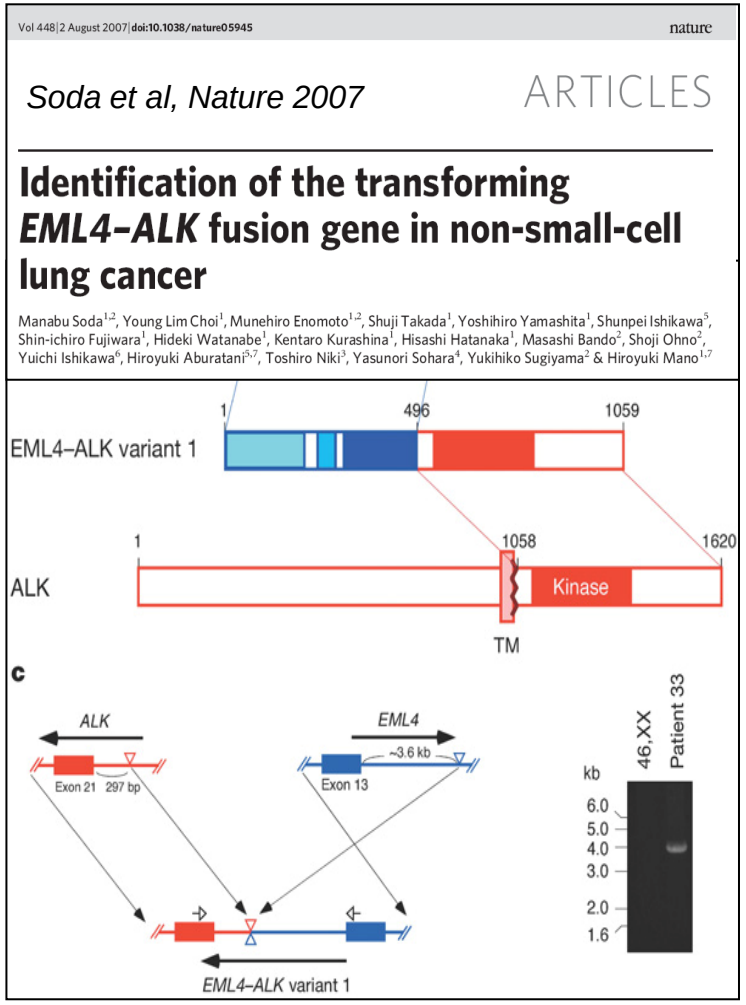
Lung Cancer in Never Smokers
EGFR Mutations in ~2,000 Adenocarcinomas



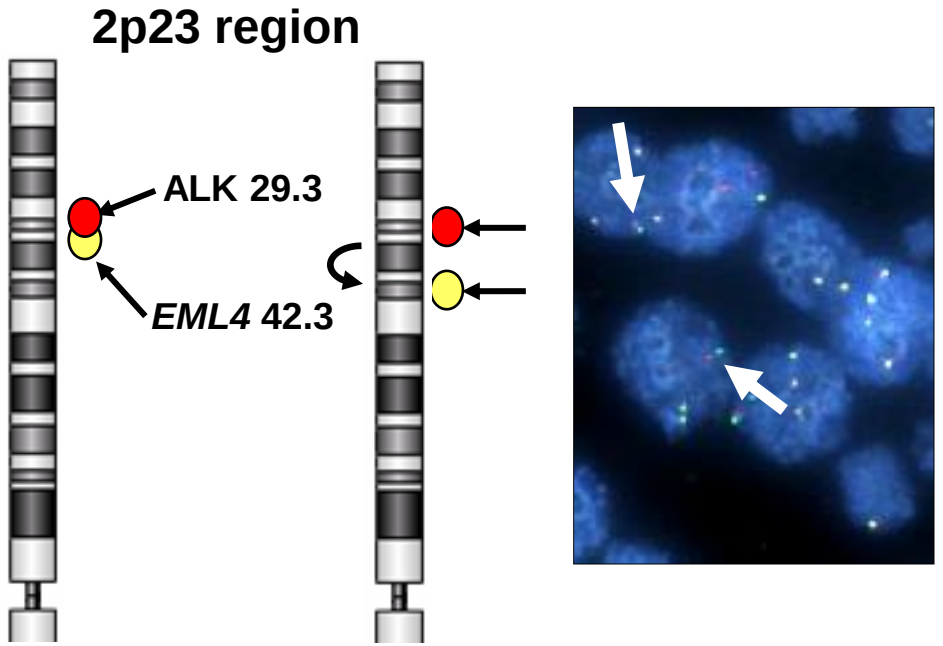
Cancer®

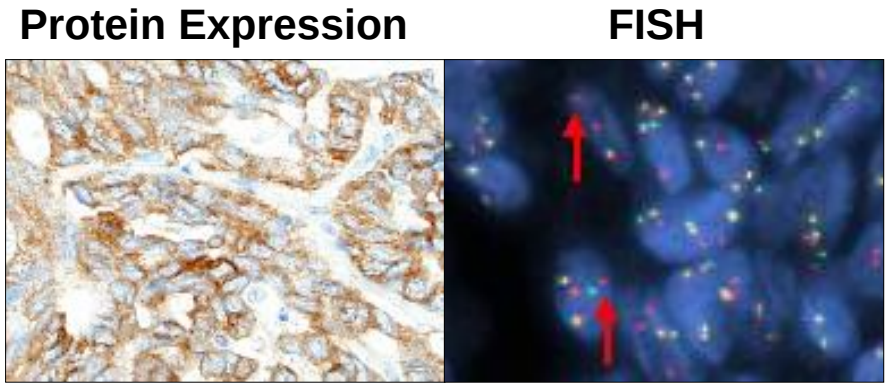
Shigematsu et al, Int J Cancer 118:257, 2006

EML4-ALK Fusion in Lung Cancer



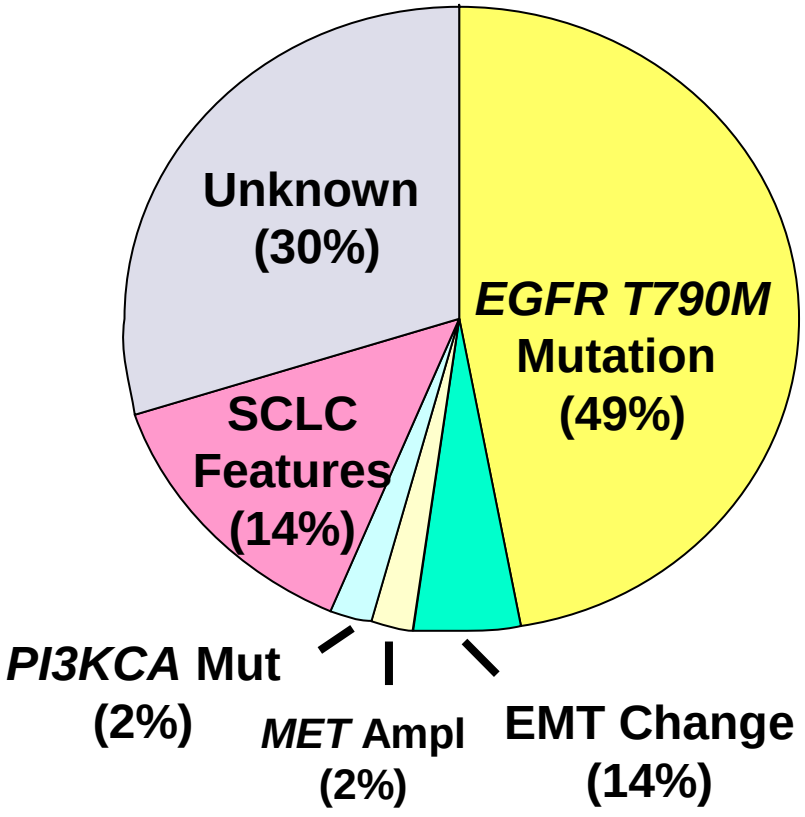
- Up to 9 variants identified





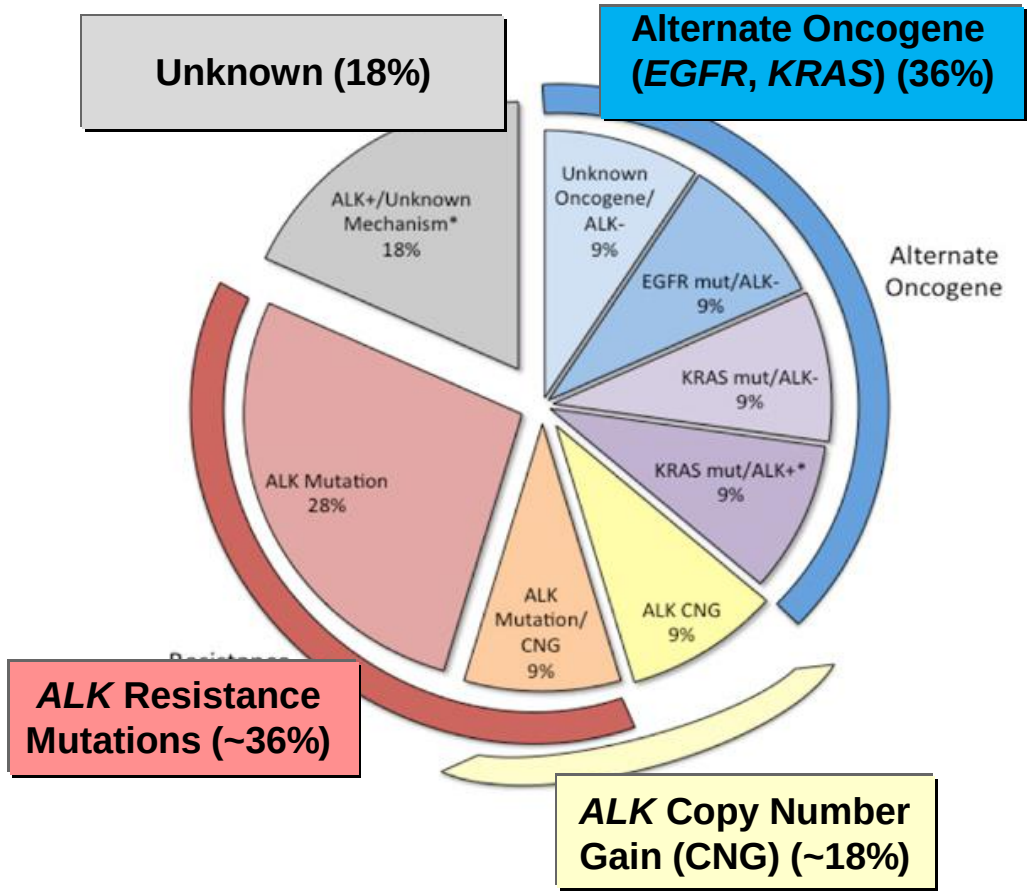
Mechanisms of Resistance to EGFR and ALK TKIs in Lung Adenocarcinoma

EGFR



Modified from Sequist L V et al. Sci Transl Med 2011;

ALK

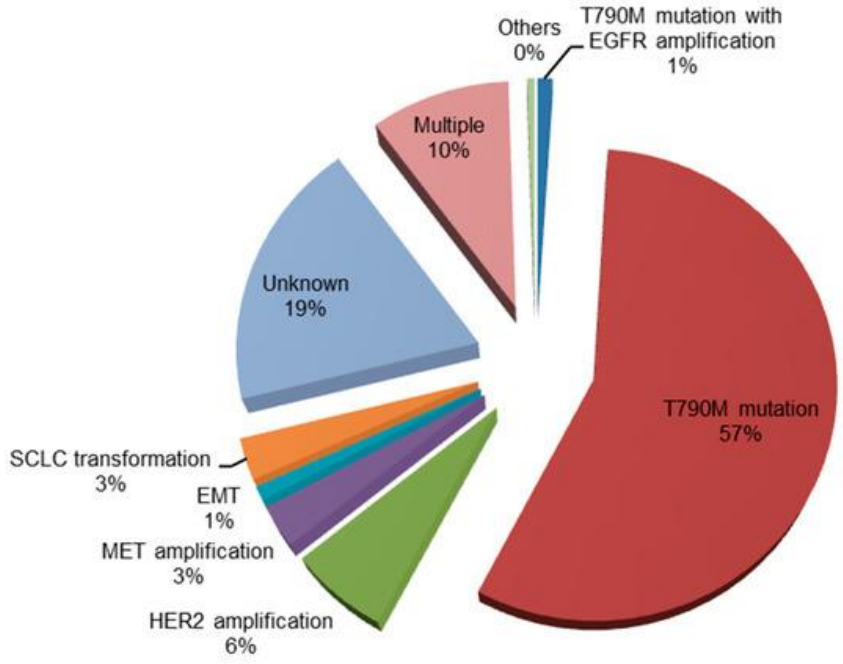


Doebele RC et al, Clin Cancer Res, 2012

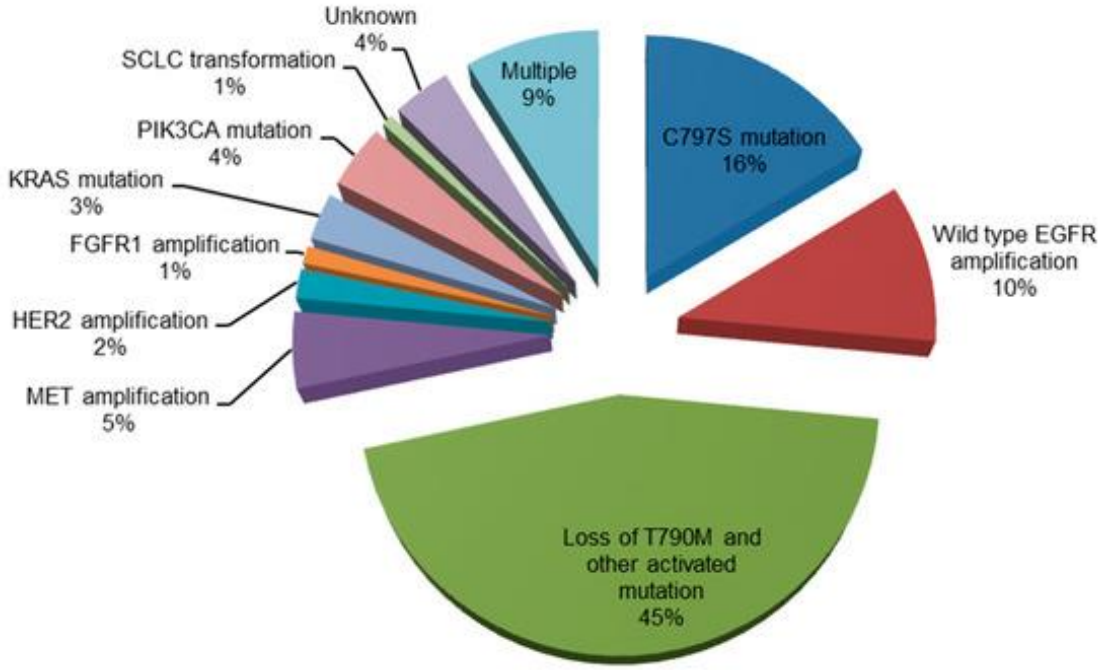
Cancer

Mechanisms of Resistance to EGFR TKIs

Acquired Resistance First-Generation



Acquired Resistance Third-Generation

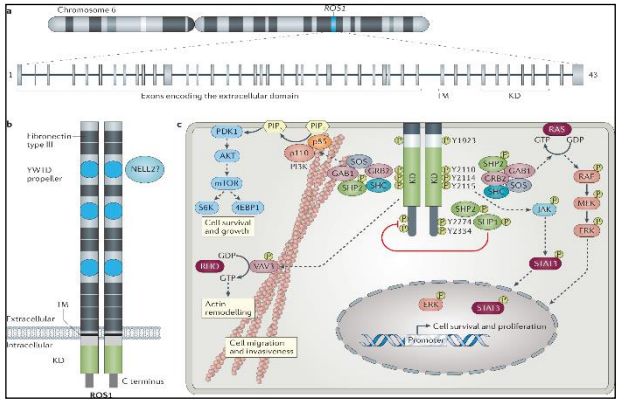


T. Nagano et al, Cells, 2018 Nov 15;7(11)

ROS1 Inhibition by in Advanced NSCLC

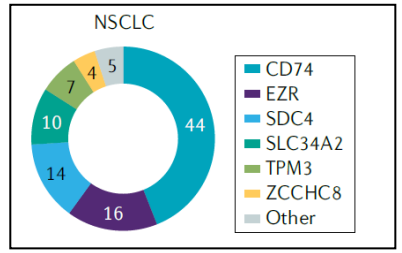
- *ROS1* share ~70% homology with *ALK*, and rearrangements have been reported in NSCLC in ~1-2%.
- In NSCLC, several *ROS1* fusion partners genes have been identified.
- *ROS1* fusion testing: IHC, FISH, RT-PCR and RNA/DNA-based NGS.

ROS1 Gene, Structure and Signaling

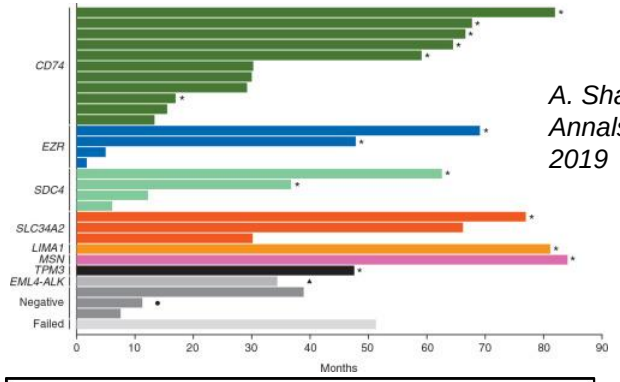


A. Drilon, Nature Reviews Clinical Oncology, 2020

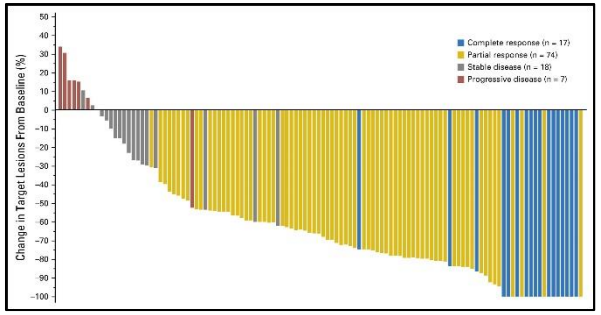
ROS1 Fusion Partner



- 53 patients with advanced NSCLC and *ROS1* fusion-positive tumors (by FISH/PCR) were treated with Crizotinib:
  - Objective Response (OR) was 72% (6 complete responses and 32 partial responses)
- 127 patients from East Asia with advanced NSCLC *ROS1* fusion-positive (by RT-PCR) treated with Crizotinib:
  - OR was 71.7% (617 complete responses and 74 partial responses)



A. Shaw et al, Annals of Oncology, 2019



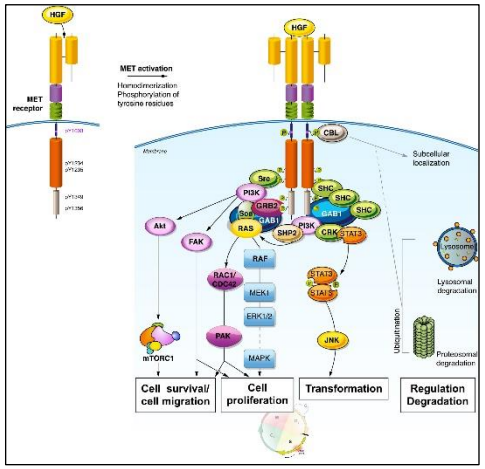
YL Wu, J Clin Oncol, 2018

Cancer

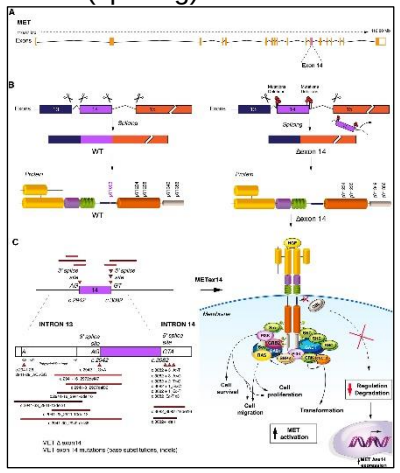
MET Inhibition by in Advanced NSCLC

- *MET gene (7q21-q31)* amplification and copy gains (≥5 or ≥10) occurs ~1-6% of NSCLC.
- *MET* exon 14 splicing mutation is detected in ~4% of NSCLC (Higher frequency reported in lung sarcomatoid carcinomas ~4%-32%).

MET activation (amplification/splicing mutation)

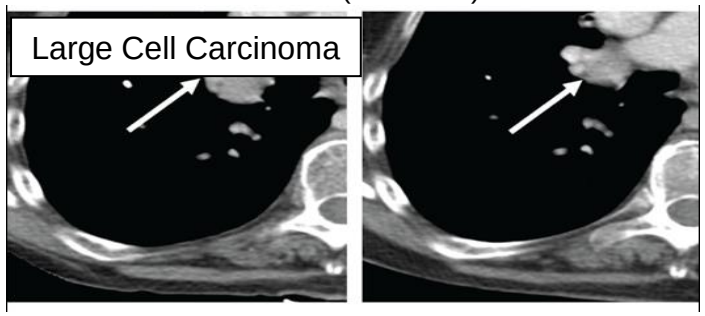


MET exon 14 skipping (splicing) mutation



A. Friedlaender et al, Cancer, 2020

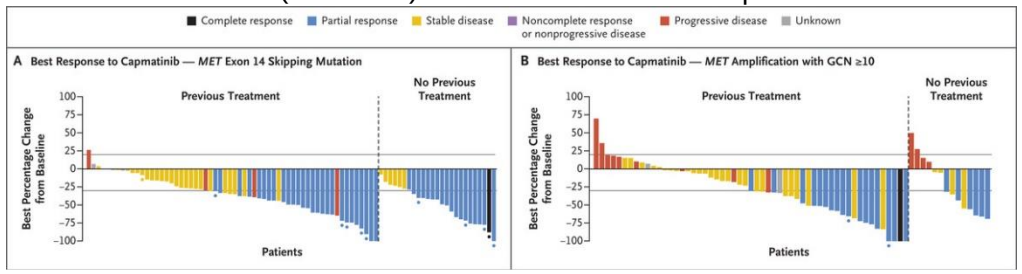
MET exon 14 (*METex14*)



- 0.6% of 38,028 tumors sequenced by FM (3% lung adenocarcinomas)
- Patients' tumor sensitive to MET inhibitor, Capmatinib

Garrett M. Frampton et al. Cancer Discovery, 2015

MET exon 14 (*METex14*) *MET* amplification



- Capmatinib showed substantial antitumor activity in advanced NSCLC with *MET exon 14* skipping mutation, particularly in not previously treated (Objective Response [OR] 68%) vs. treated (OR 41%)
- Capmatinib efficacy in *MET*-amplified advanced NSCLC was higher in tumors with a high gene copy number (≥10 copies); higher in not treated previously (OR 40%) vs. treated (OR 29%

J Wolf et al. N Engl J Med, 2020

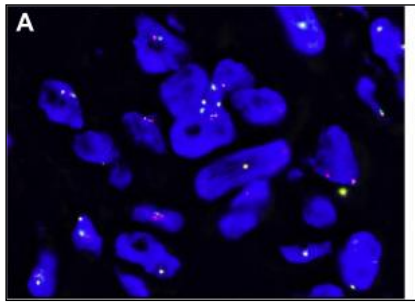
Cancer

RET Inhibition by in Advanced NSCLC

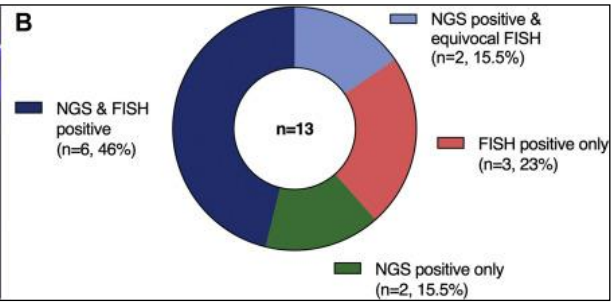
- *RET* gene fusions occur in 1.4 of NSCLC and 1.7% of lung adenocarcinomas.
- *RET* rearrangements involve at least 12 gene partners, being *KIF5B* the most frequent.

RET Fusion Testing

RET FISH

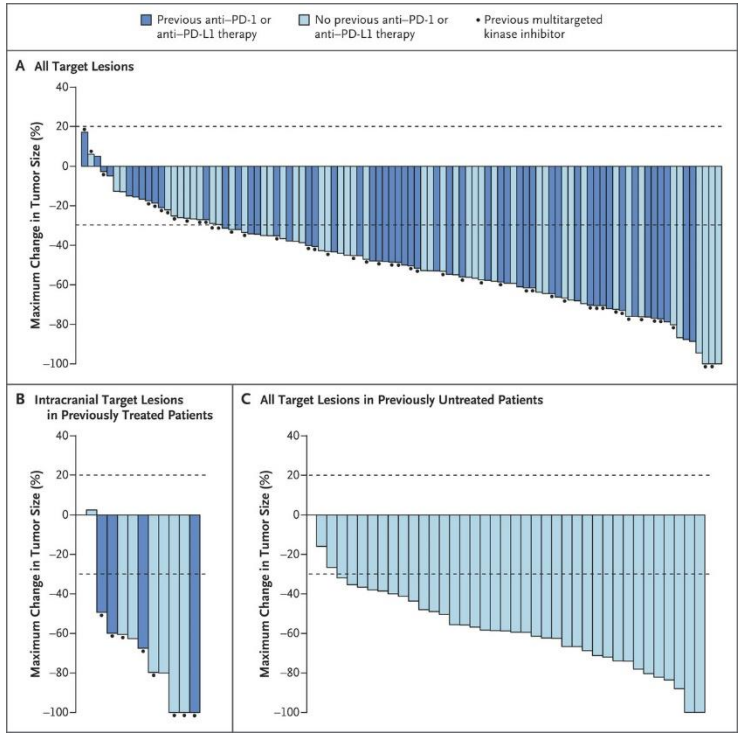


Concordance between FISH and NGS



A, Tan et al, Journal of Thoracic Oncology, 2020

- 105 NSCLC patients were treated with Selpercatinib, a highly selective small-molecule inhibitor RET kinase.
- Diagnosis was made by NGS testing in tissue (n=85) and blood (n=9) using FISH (n=9) and PCR (n=2).
- Patients treated had durable efficacy, including intracranial activity, in patients with *RET* fusion-positive NSCLC (both untreated [Objective Response, OR 85%] and previously treated [OR 64%]).



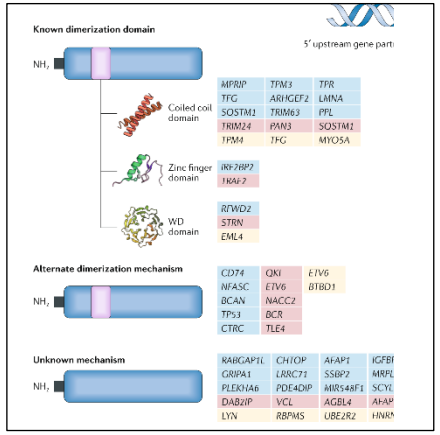
A. Drilon et al. N Engl J Med 2020

Cancer

NTRK Inhibition by in Advanced NSCLC

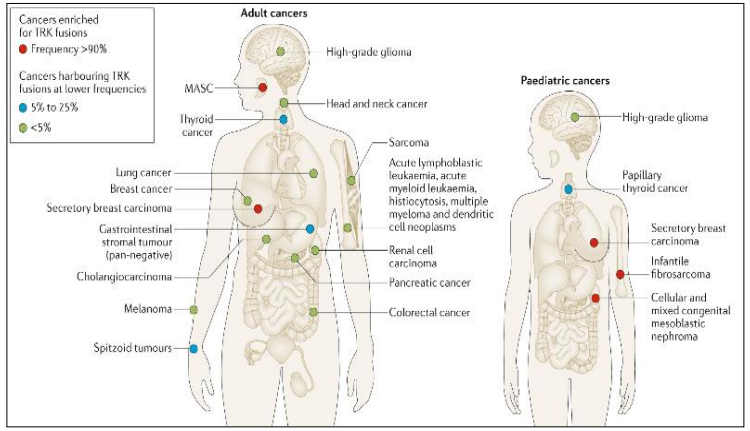
- Tropomyosin-related kinase (TRK) encodes a tyrosine kinase receptor for neurotrophins.
- Gene arrangements (1% of NSCLCs) can occur in the 3 members of this family *NTRK1*, *2* and *3* genes.

Activating Mechanisms of *NTRK* Fusions

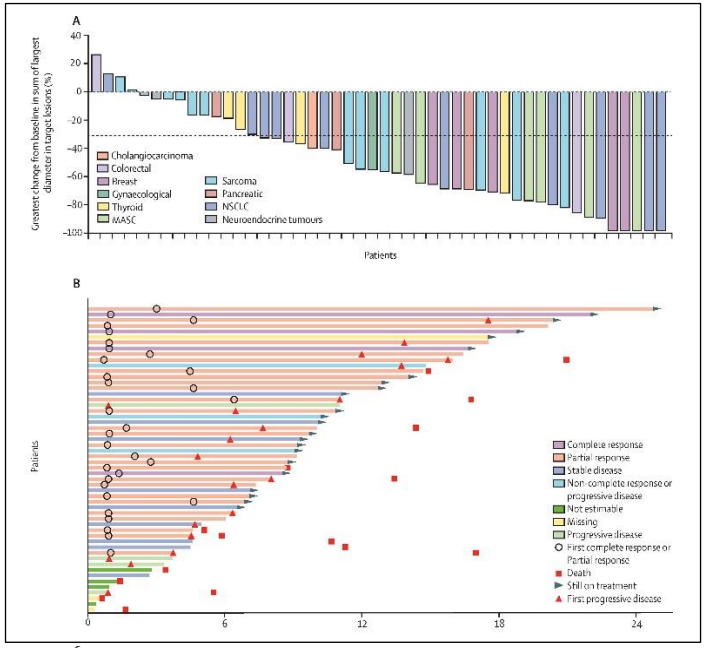


E. Cocco et al, Nature Reviews C

Distribution of *NTRK* Fusions



- Analysis of 3 phase 1-2 clinical trials using Entrectinib, a potent TRK inhibitor in 54 patients with advanced/metastatic *NTRK* fusion-positive solid tumors (10 sites/19 histologies; 10 NSCLC).
  - 31 patients (57%) had an Objective Response (OR)
  - 4 (7%) had complete response, and 27 (50% had a partial response.
  - 7 our of 10 (70%) of NSCLC had a OR.

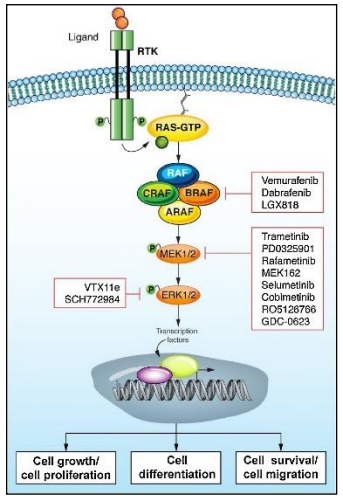


R. Doebele et al, Lancet Oncol, 2020

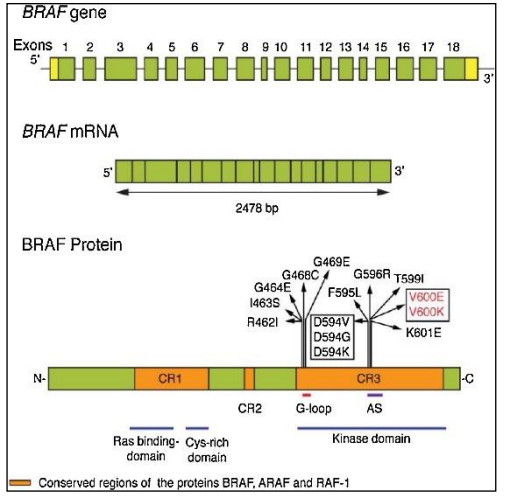
BRAF Inhibition by in Advanced NSCLC

- *BRAF* mutations have been identified in solid tumors, including melanoma, colon and lung cancer.
- *BRAF V600E* is the most frequent mutation in this gene, with a frequency of ~3% in NSCLC.
- In NSCLC, it has been associated to adenocarcinoma histology and smoking status.

MAPK Signaling Pathway

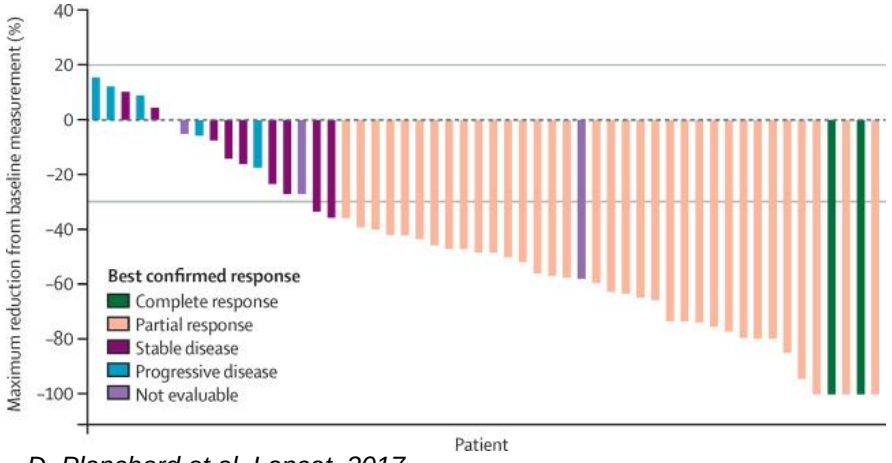


BRAF Gene and Point Mutations



D. Frisone, Critical Reviews in Oncology, 2020

- 53 advanced *BRAF V600E*-mutant NSCLC with tumor progression were treated with BRAF and MEK (dabrafenib and trametinib) inhibitors and 36 (63.2%) achieved OR.
- There are less data available with non-*V600E* mutations.

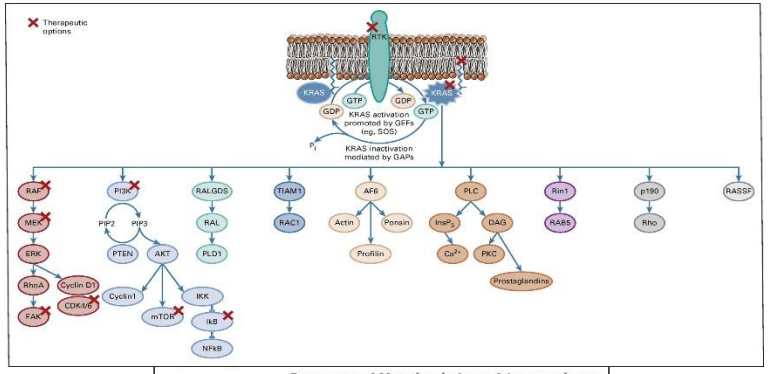


D. Planchard et al, Lancet, 2017

Cancer

KRAS^{G12C} Inhibition by in Advanced NSCLC

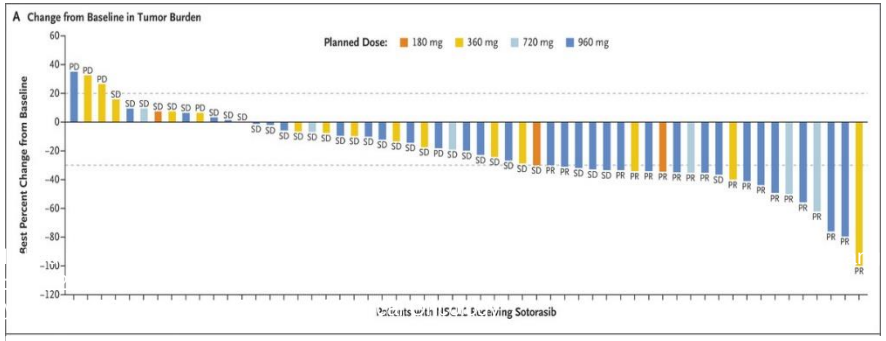
- *KRAS* mutations occur in ~30% and *KRAS*^{G12C} mutations occur in ~12-14% of lung adenocarcinomas (mostly smokers)
- N=59 NSCLC patients with advanced tumors treated with Sortorasib a *KRAS*^{G12C} inhibitor
  - 32% objective response
  - 88% disease control
- Median progression free survival is 6.3 months

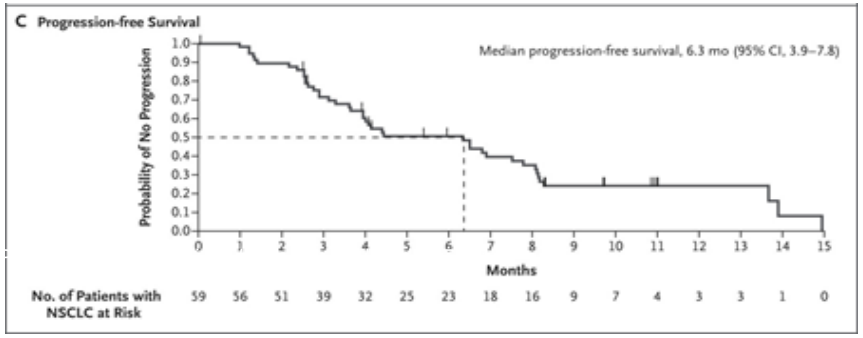


Mutation	Frequency of Mutation in Lung Adenocarcinoma Across Data Sets, Range (%)
G12C	41.4-55.3
G12A	6.1-12.1
G13C	6.4-12.1
G12V	10.6-26.5
G12D	6.1-12.1
Q61L	1.7-2.0
Q61H	4.3[a]
G12R	1.7[a]
G12S	2.1-4.1
G13D	3.5-8.5
K88	2.0[a]

[a]Only reported in a single data set.

TF Burns et al, Journal of Clinical Oncology 2020





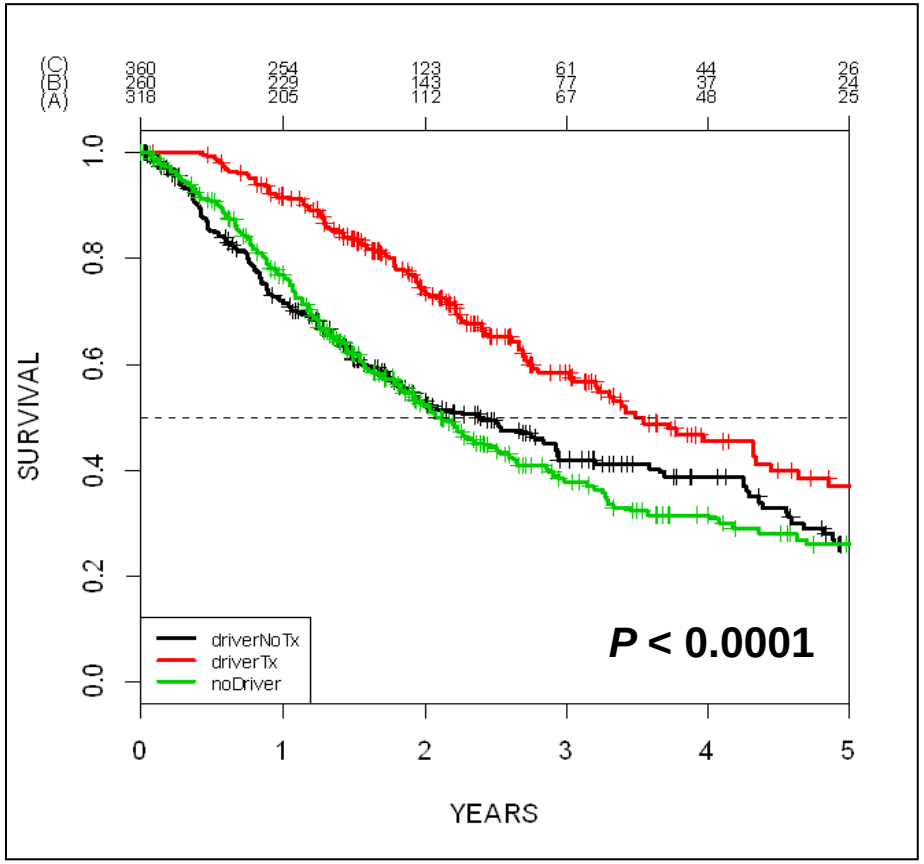
DS Hong et al. N Engl J Med 2020;383:1207-1217.

Lung Cancer Mutation Consortium-1 (LCMC-1)

1,000 Adenocarcinomas
13 US Institutions

<u>Mutations</u> (8 genes/115 Assays)
Sequenom™ and Snap Shot™
- ***AKT1***
- ***BRAF***
- ***EGFR***
- ***HER2***
- ***KRAS***
- ***MEK1***
- ***NRAS***
- ***PIK3CA***

<u>FISH</u> (2 genes)
- ***MET* amplification**
- ***EML4-LK* fusion**



Group	N	Median Survival Yrs. (95% CI)
Driver, no targeted therapy (A)	318	2.4 (1.9-2.9)
Driver, targeted therapy (B)	260	3.6 (3.1-4.5)
No driver (C)	360	2.2 (1.8-2.5)

Cancer

M Kris et al , JAMA, 2014

Comparison of NGS with Conventional Sequencing Technologies

Platform	Sensitivity (for clinical use)	Sample Requirement	Multiplexing Capability	Throughput	Type of Changes	Quantitative
Sanger	20%	High	None	Low	SNV, indel	No
Pyro-	5%	Intermediate	None	Low	SNV	Yes
Sequenom/ ABI SNaPshot	5-10%	Intermediate	Intermediate	Medium	SNV	Yes
NGS	1-5%	Low	High (amplicons and samples)	High	SNV, indel, fusion, CNV	Yes

SNV: single nucleotide variations
CNV: copy number variations
Indels: insertions/deletions

Cancer

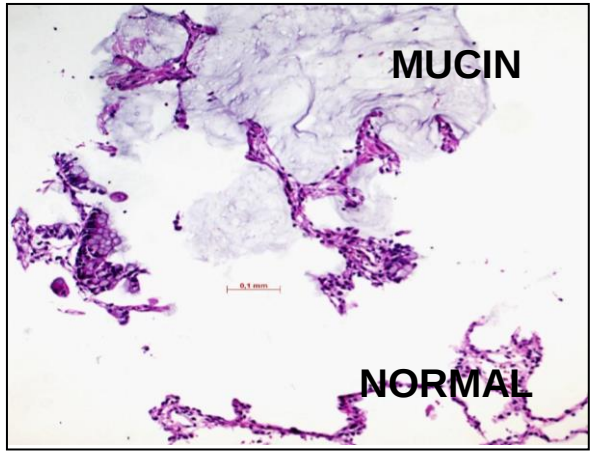
Courtesy of Raja Luthra, PhD, MD Anderson Cancer Center

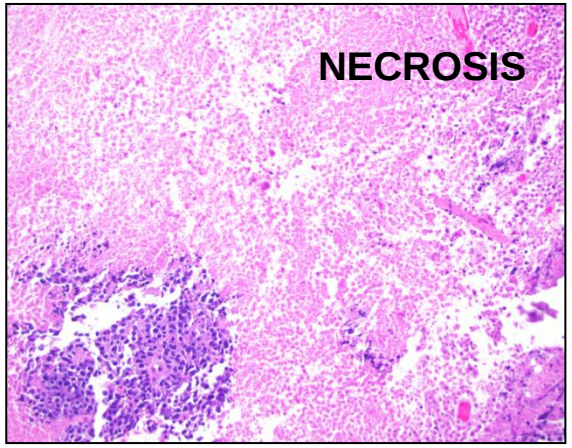
Next-Generation Sequencing (NGS) Panel - Major Benefits

- Provide information in multiple targetable gene abnormalities.
- Data on mutation, copy number variations, indels and translocations
- Can be performed in routine small FFPE tissue samples and liquid biopsy (cfDNA, CTCs, exosome DNA).
- Turn around time acceptable for clinical management and costs being significantly reduced.
- Clinically, it offers to patients more options to get off-label treatment and enter in genomic-based clinical trials.
- May provide information on tumor mutational burden (TMB), and immune-suppressive genotypes (e.g., *LKB1* mutations)

Quality of Tumor Sample for Molecular Testing

- Is there a homogenous tumor cell population?
- Are the tumor cells viable?
- Is there background necrosis, inflammation or too much normal tissue?





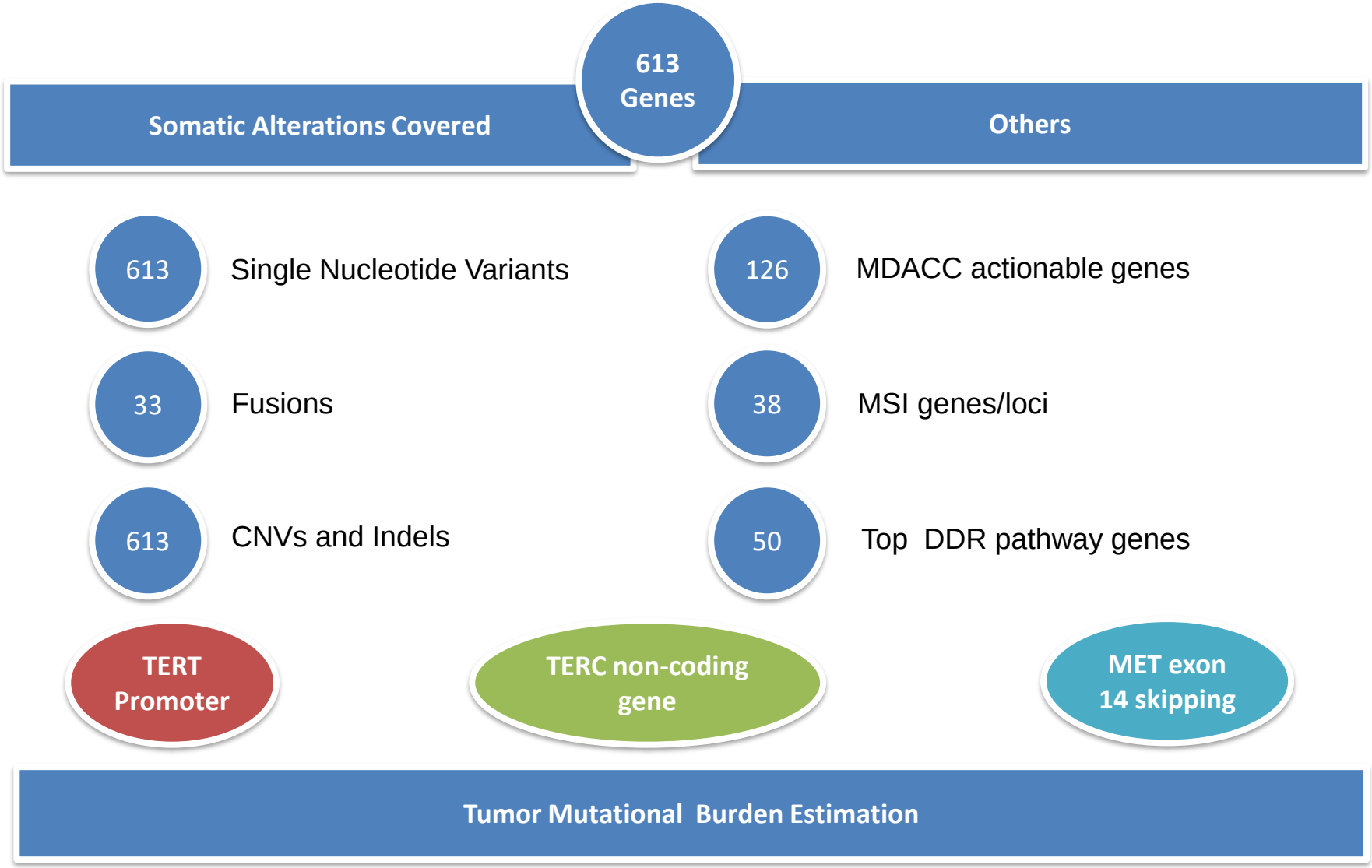
NGS for Mutation Analysis Samples Using FFPE Tumor Tissues

Oncomine Comprehensive Assay v3 – 161 Genes (at MD Anderson Cancer Center)

Hotspot Genes				Full-length Genes			Copy Number Genes		Gene Fusions (Inter- and Intragenic)		
AKT1	FOXL2	MET	AKT2	ATM	TP53	MSH6	AKT1	PPARG	ALK	RET	NF1
ALK	GATA2	MTOR	AKT3	BAP1	TSC1	NBN	AR	TERT	AXL	ROS1	NOTCH1
AR	GNA11	MYD88	AXL	BRCA1	TSC2	NOTCH2	CCND1	AKT2	BRAF	AKT2	NOTCH4
ARAF	GNAQ	NFE2L2	CCND1	BRCA2	ARID1A	NOTCH3	CCNE1	AKT3	EGFR	AR	NRG1
BRAF	GNAS	NRAS	CDK6	CDKN2A	ATR	PALB2	CDK4	ALK	ERBB2	BRCA1	NTRK2
BTK	HNF1A	PDGFRA	ERCC2	FBXW7	ATRX	PMS2	CDK6	AXL	ERG	BRCA2	NUTM1
CBL	HRAS	PIK3CA	FGFR4	MSH2	CDK12	POLE	EGFR	BRAF	ETV1	CDKN2A	PDGFRB
CDK4	IDH1	PPP2R1A	H3F3A	NF1	CDKN1B	RAD50	ERBB2	CCND2	ETV4	ERBB4	PIK3CA
CHEK2	IDH2	PTPN11	HIST1H3B	NF2	CDKN2B	RAD51	FGFR1	CCND3	ETV5	ESR1	PRKACA
CSF1R	JAK1	RAC1	MAP2K4	NOTCH1	CHEK1	RAD51B	FGFR2	CDK2	FGFR1	FGR	PRKACB
CTNNB1	JAK2	RAF1	MDM4	PIK3R1	CREBBP	RAD51C	FGFR3	CDKN2A	FGFR2	FLT3	PTEN
DDR2	JAK3	RET	MYC	PTCH1	FANCA	RAD51D	FGFR4	CDKN2B	FGFR3	JAK2	RAD51B
EGFR	KDR	RHEB	MYCN	PTEN	FANCD2	RNF43	FLT3	ESR1	NTRK1	KRAS	RB1
ERBB2	KIT	RHOA	NTRK1	RB1	FANCI	SETD2	IGF1R	FGF19	NTRK3	MDM4	RELA
ERB83	KNSTRN	SF3B1	NTRK2	SMARCB1	MLH1	SLX4	KIT	FGF3	PDGFRA	MET	RSPO2
ERBB4	KRAS	SMO	PDGFRB	STK11	MRE11A	SMARCA4	KRAS	NTRK1	PPARG	MYB	RSPO3
ESR1	MAGOH	SPOP	PIK3CB				MDM2	NTRK2	RAF1	MYBL1	TERT
EZH2	MAP2K1	SRC	ROS1				MDM4	NTRK3			
FGFR1	MAP2K2	STAT3	SMAD4				MET	PDGFRB			
FGFR2	MAPK1	U2AF1	TERT				MYC	PIK3CB			
FGFR3	MAX	XPO1	TOP1				MYCL	RICTOR			
FLT3	MED12						MYCN	TSC1			
							PDGFRA	TSC2			
							PIK3CA				

https://assets.thermofisher.com/TFS-Assets/LSG/brochures/oncomine-comprehensive-assay-v3-flyer.pdf

MD Anderson New NGS Panel Content



FDA approves pembrolizumab for adults and children with TMB-H solid tumors

On June 16, 2020, the Food and Drug Administration granted accelerated approval to pembrolizumab (KEYTRUDA, Merck & Co., Inc.) for the treatment of adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options.

Today, the FDA also approved the FoundationOneCDx assay (Foundation Medicine, Inc.) as a companion diagnostic for pembrolizumab.

Efficacy was investigated in a prospectively-planned retrospective analysis of 10 cohorts of patients with various previously treated unresectable or metastatic TMB-H solid tumors enrolled in a multicenter, non-randomized, open-label trial, KEYNOTE-158 (NCT02628067). Patients received pembrolizumab 200 mg intravenously every 3 weeks until unacceptable toxicity or documented disease progression.

Comparison of Available NGS Assays that Generate TMB Score

Definition: TMB is the total number of mutations per coding area of a tumor genome (usually represented by N mutations/genome megabase).

Assay	Total size/ Coding (Mb)	Aberration in Algorithm*	Germline Filtering	Cancer Gene Bias Correction	FFPE Error Correction	Targeting
MSK-Impact	1.5/1.14	SNV (nonsyn), indels	Paired normal	No	Pool of normals	Hybrid capture
FoundationOne CDx	2.2/0.8	SNV (non+syn), indels	Database, SGZ	Yes	Bioinformatic	Hybrid capture
TSO500	1.9/1.3	SNV (non+syn), indels	Database, SGZ	Yes	UMI	Hybrid capture
Thermo Fisher Oncomine	1.7/1.2	SNV (missense, nonsense) >5% AF	Database	No	UDG; Deamination metric	Amplicon
Qiagen	1.3/1.3	SNV (nonsyn), indels	Database	No	UMI	Amplicon

* Aberrations included in bioinformatic pipeline to estimate TMB. All assays report TMB according to definition i.e. NS-TMB per Mb correlated to WGS.

Lyntte Sholl et al (IASLC Pathology Committee), J Thoracic Oncol, 2020

Tumor Mutation Burden (TMB) and IO Response in NSCLC

- TMB is the number of somatic mutations derived from NGS techniques.
- A large number of clinical trials and retrospective analyses have shown a correlation between high TMB (tissue and blood) and immune checkpoint inhibitor response rates and PFS.
- Many challenges remain prior to implementation of TMB as a biomarker in clinical practice:
  - Identification of therapies whose response is best informed by TMB status
  - Robust definition of a predictive TMB cut-point.
  - Acceptable NGS panel size and design.
  - Need for robust technical and informatic rigor to generate precise and accurate TMB measurements across different laboratories.

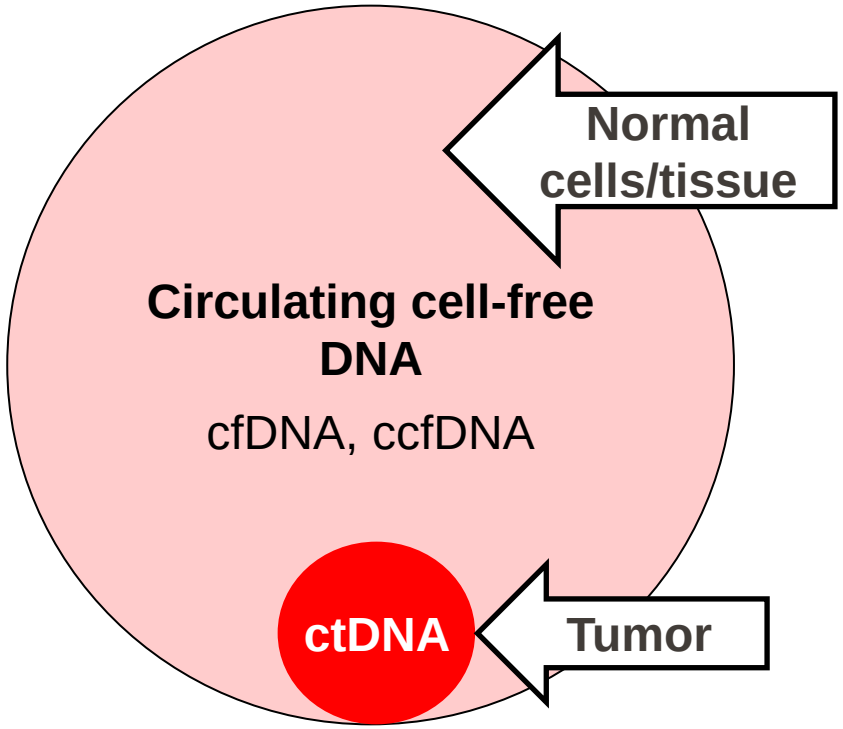
Lyntte Sholl et al (IASLC Pathology Committee), J Thoracic Oncol, 2020.

Liquid Biopsy in Lung Cancer

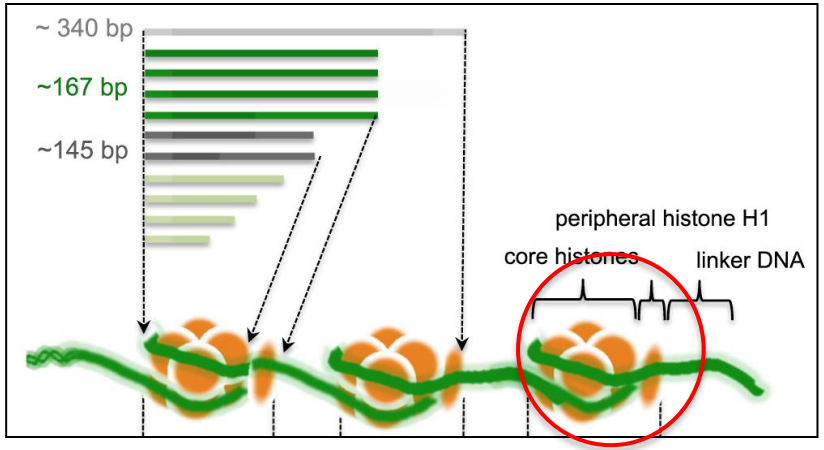
- Currently, it is used in metastatic disease to deliver targeted therapy:
  - Can be easily repeated to control treatment efficiency and/or the detection of genomic changes resulting from resistance to therapy (e.g., *EGFR T790M*)
  - It is an alternative to patients with solid tumors when biopsies are inaccessible or after more than one attempt the yield was unsatisfactory

- Other applications:
  - Tumor mutational burden (TMB)
  - Monitoring response to immunotherapies
  - Minimal residual disease (MRD)
  - Early detection

Characteristics and Terminology for Circulating Tumor DNA (ctDNA)



167 bp fragments of DNA, a nucleosome



The linker DNA between nucleosomes is cleaved leaving 167 bp cell-free DNA fragments (145 bp plus a ~20 bp segment wrapping histone H1). Originally described by Wyllie in 1980.

Chandrananda et al. 2015 BMC Medical Genomics.
Wyllie 1980 Nature

Slide courtesy of Dr. Rick Linman, MD

cfDNA Genotyping Analysis

Blood

cfDNA

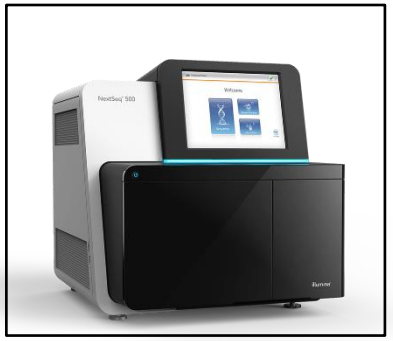
Pre-analytical Issues

Plasma

- Amount of blood/plasma
- Type of tubes
- Time for processing

Next Generation of Sequencing (NGS)

Ion Proton
(Thermo Fisher)



Next-Seq
(Illumina)

Large/ Intermediate Panels

PCR-base Methods

Didigal Droplet (dd)PCR (Biorad)

qPCR
(Cobas)

Small Panels/ Single Genes

Liquid Biopsy Panel-70 (LBP-70)

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

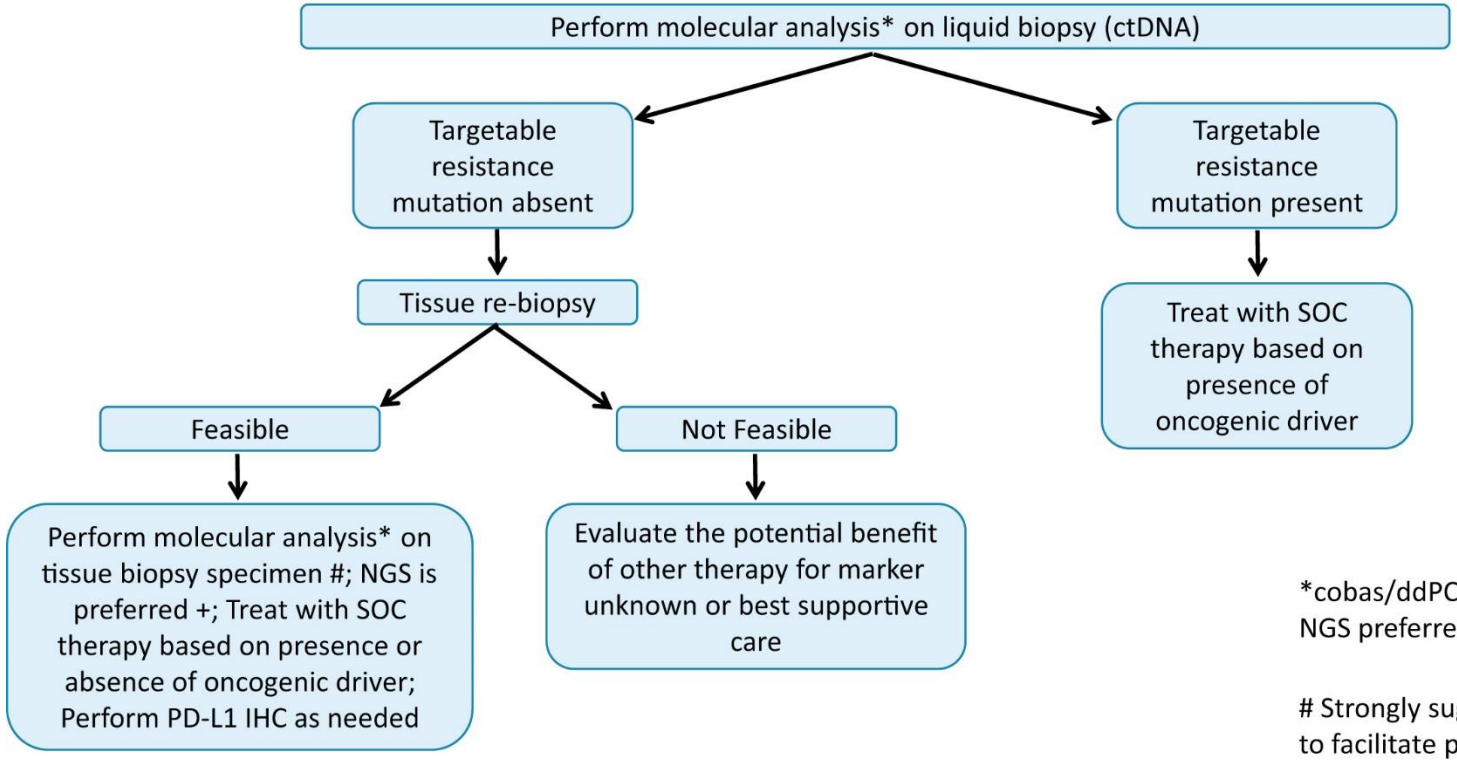
Liquid Biopsy Panel-70 (LBP-70)

Mutations (SNVs, Indels); N= 70 Genes
Amplifications (CNVs); N=19: ●
Fusions; N=6 ▲
Unique to MD Anderson Panel: €

AKT1	FGFR2 ● ▲	NOTCH1
ALK ▲	FGFR3 ● ▲ €	NOTCH2 €
APC	GNA11	NPM1
AR ●	GNAQ	NRAS
ARAF	GNAS	NTRK1 ▲
ARID1A	HNF1A	NTRK3
ATM	HRAS	PDGFRA ●
BRAF ●	IDH1	PIK3CA ●
BRCA1	IDH2	PTEN
BRCA2	JAK2	PTPN11 €
CCND1 ●	JAK3	RAD51 €
CCND2 ●	KIT ●	RAF1 ●
CCNE1 ●	KRAS ●	RB1
CDK4 ●	MAP2K1	RET ▲
CDK6 ●	MAP2K2	ROS1 ▲
CDKN2A	MAPK1	SMAD4
CTNNB1	MAPK3	SMO
DDR2	MET ●	STK11
EGFR ●	MLH1	TERT
ERBB2 ●	MPL	TP53
ESR1	MTOR	TSC1
EZH2	MYC ●	VHL
FBXW7	NF1	
FGFR1 ●	NFE2L2	

Molecular Testing in Patients with Progression or Recurrent Disease During Treatment with TKI

Patient with NSCLC progressive or recurrent disease during treatment with TKI



*cobas/ddPCR for *EGFR* mutation
NGS preferred for *ALK* and *ROS1*

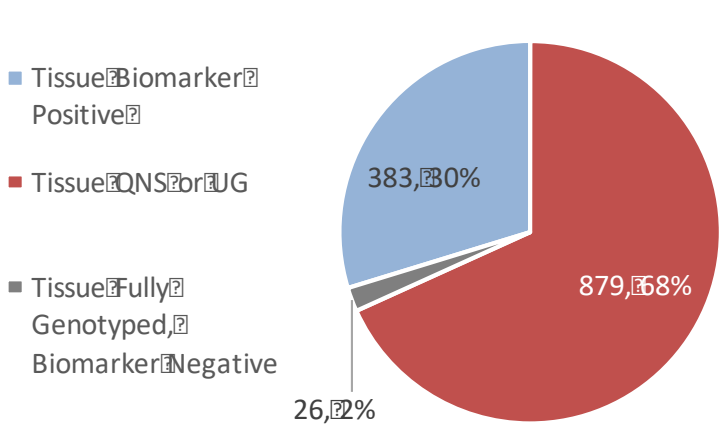
Strongly suggest tissue sparing to facilitate participation in clinical trials

+ While NGS is preferred, based on availability, other validated assays are acceptable

Cancer

J Thorac Oncol. 2018 Sep;13(9):1248-1268

ctDNA Utility in Under-Genotyped Non-squamous NSCLC

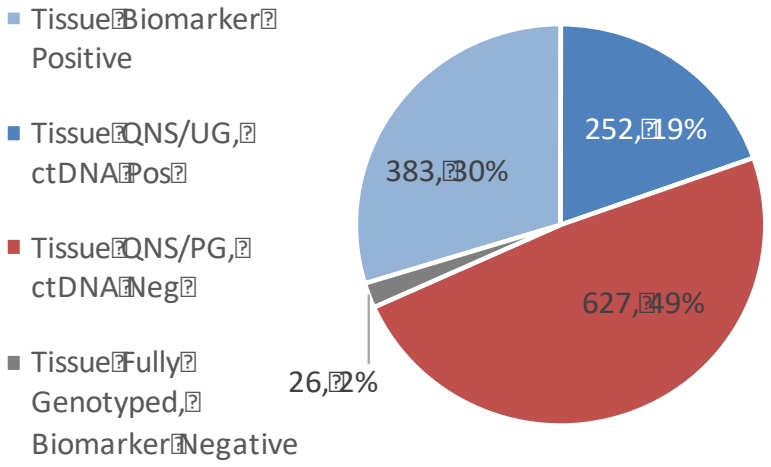


Biomarker	N in Tissue
EGFR	256
KRAS	61
ALK fusion	27
ROS1 fusion	9
RET fusion	4
BRAF V600E	10
MET amp	10
MET E14	4
HER2 mutation	1
FGFR3 fusion	1
TOTAL	**383**

Tissue Genotyping Status

383 of 1288 (30%) Biomarker Positive

879 (68%) Quantity Insufficient (QNS) or Undergenotyped (UG)



Biomarker	N in ctDNA*
EGFR	42
KRAS	127
ALK fusion	3
ROS1 fusion	2
RET fusion	14
BRAF V600E	13
MET amp	23
MET E14	7
HER2 mutation	21
TOTAL	**252**

ctDNA NGS Increased Biomarker Yield by 65%

ctDNA analysis identified 252 *additional* actionable biomarkers (19% of 1288) not previously detected in tissue QNS/UG cases

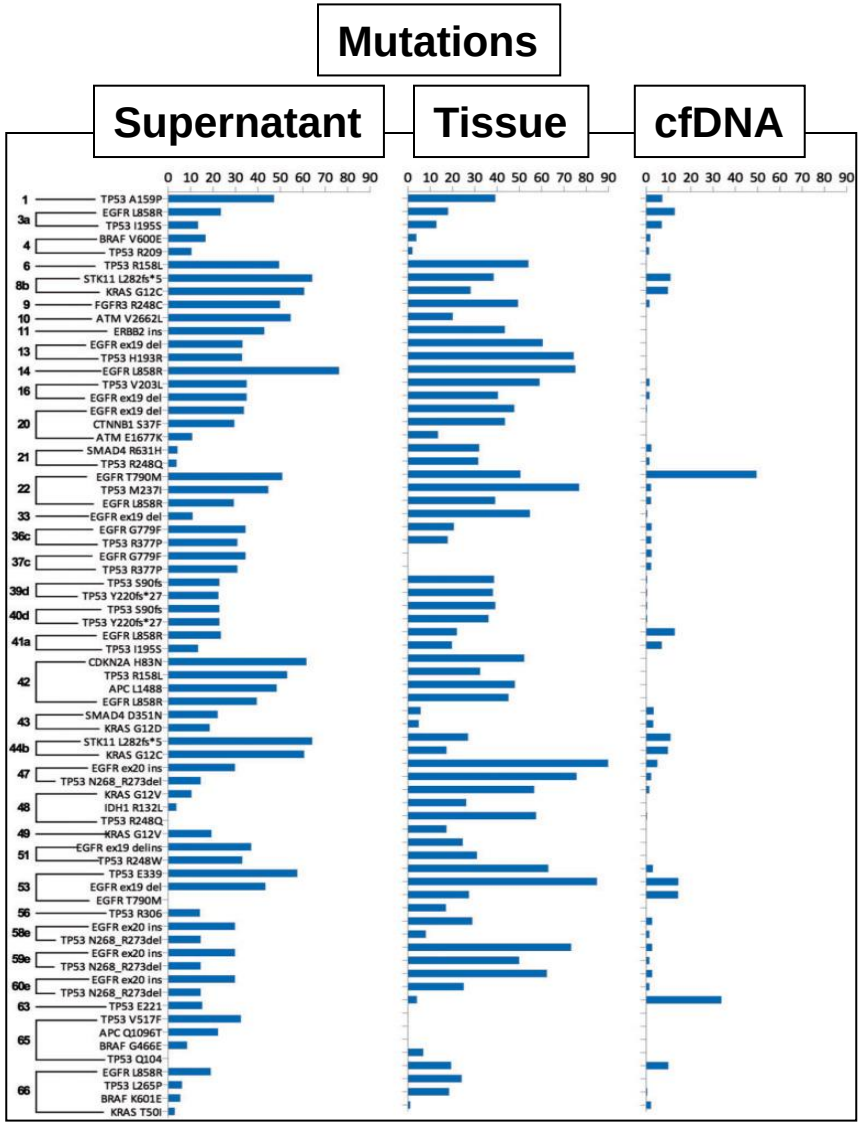
Cancer

Slide courtesy of David Gandara, MD, UC Davis, USA

Zill et al, CCR 2018

cfDNA Assay fo Lung Cancer Using Centrifuged Supernatants from FNAs

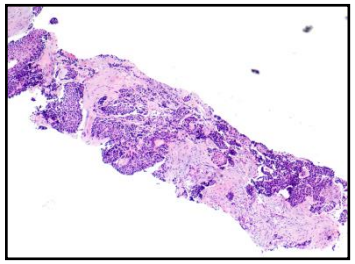
- From 150 lung cancer FNAs, all cases yielded enough DNA and 104 (90%) provided successful results by NGS and ddPCR.
- Somatic mutations were detected in 82% of samples and relevant clinical mutations in 50%.
- There was a high concordance between mutation profiles of 67 cases with tissue available: 100% with concurrent FNA tissue/cells and 96% with core needle biopsies (96%).
- In 45 cases with plasma cfDNA samples concordance of driver mutations was 84%



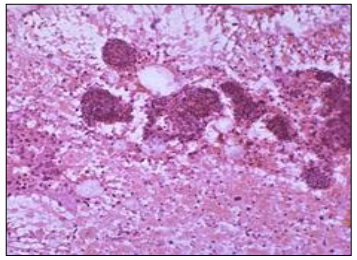
Cancer

Hannigan, et al, Annals of Oncology, 2019

Diagnostic Algorithm for Lung Cancer Diagnosis



Biopsy

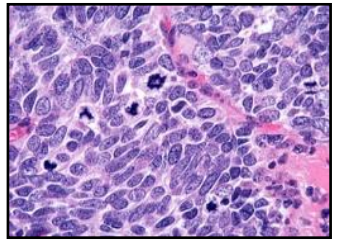


Cytology

Blood

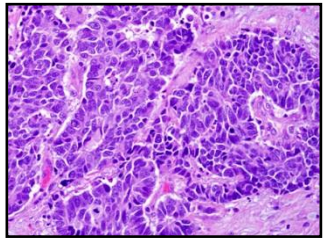
cfDNA Testing
(Liquid Biopsy)
TMB?

SCLC



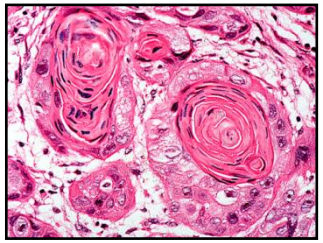
Morphology

LCNEC



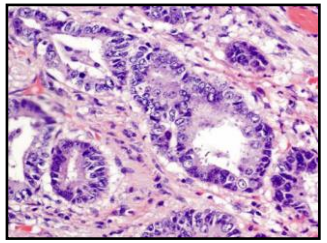
Morphology
IHC NE (+)

Squamous



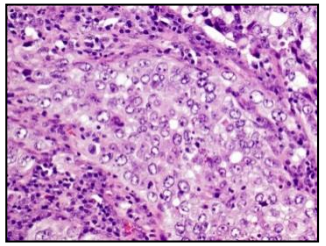
Morphology
IHC p63/p40 (+)

Adenoca



Morphology
IHC TTF1 (+)

NSCLC-NOS



Morphology
IHC (-)

***EGFR* and *BRAF* mutation, *ALK*, *ROS1* and *NTRK* fusions, *MET ex14* splicing**

PD-L1 IHC

Tumor Mutational Burden (TMB)

Thank You

Cancer