

# The characterization of lung cancer: molecular and pathway analysis

# Jean-Charles SORIA, MD, PhD



# Disclosure Slide

- ❖ Consultancy fees from

- Abbott, Amgen, AstraZeneca, BMS, EOS, GSK, Lilly, Merck-Serono, MSD, Pfizer, Roche-Genentech, Sanofi.

- ❖ My talk will focus on NSCLC

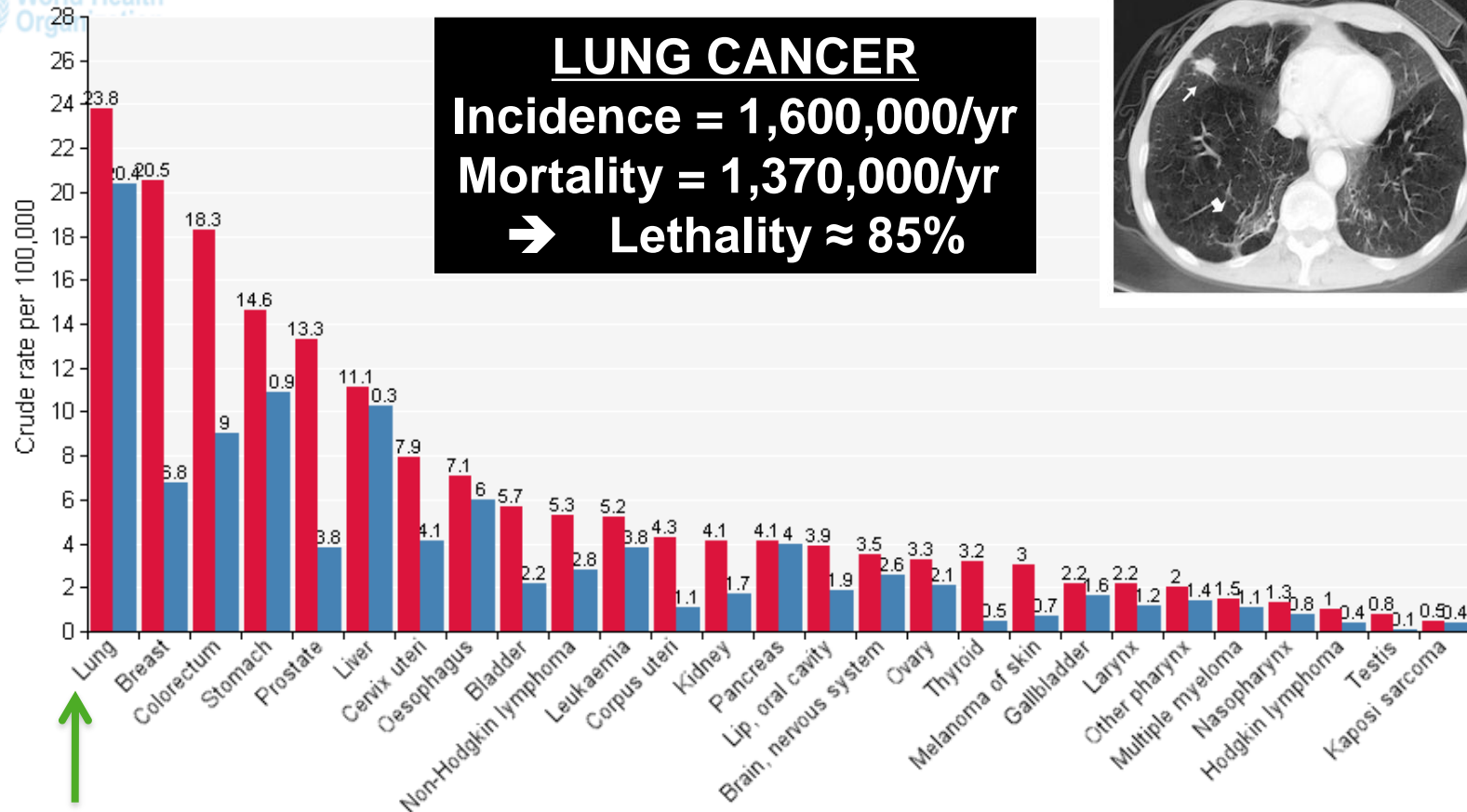
# Overview

- ❖ Lung cancer from histology to biology
- ❖ Molecular classification of adenocarcinomas
- ❖ Molecular classification of squamous cell carcinomas
- ❖ Towards an integrative approach
  - clonal architecture, new targets and resistance mechanisms
  - DNA repair complexity and related biomarkers
  - biomarkers of activity of immunotherapies

# World Cancer Incidence and Mortality

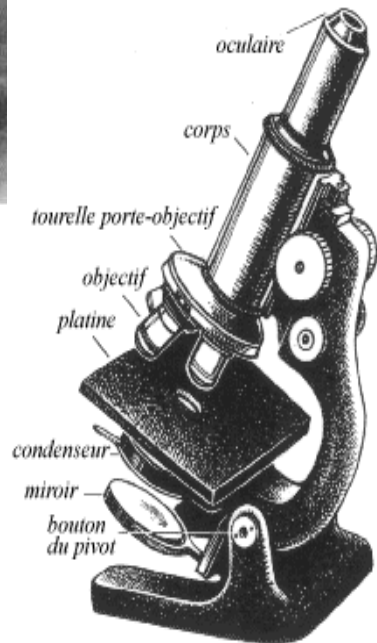
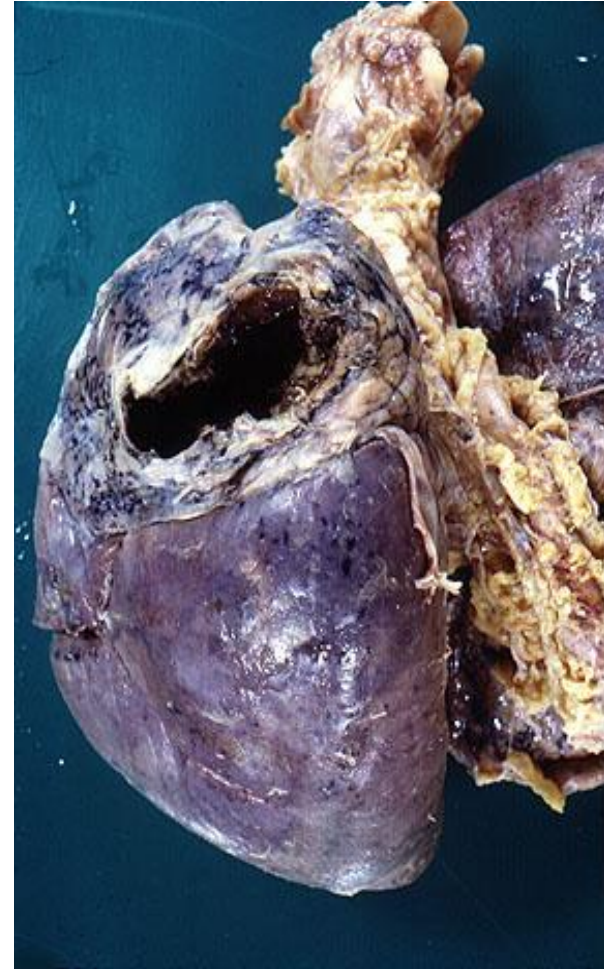
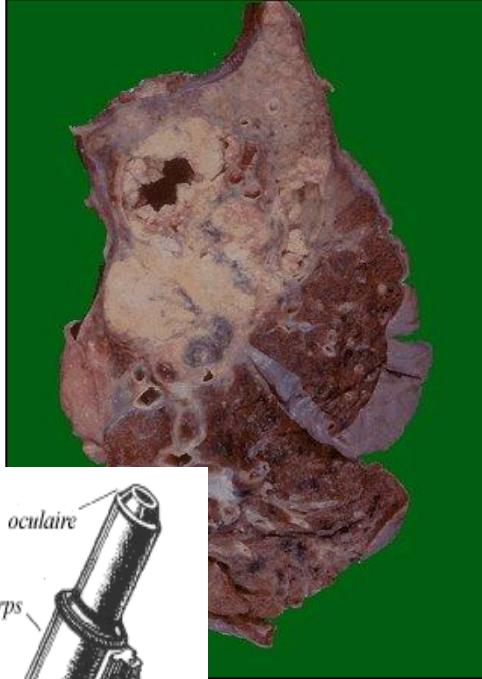
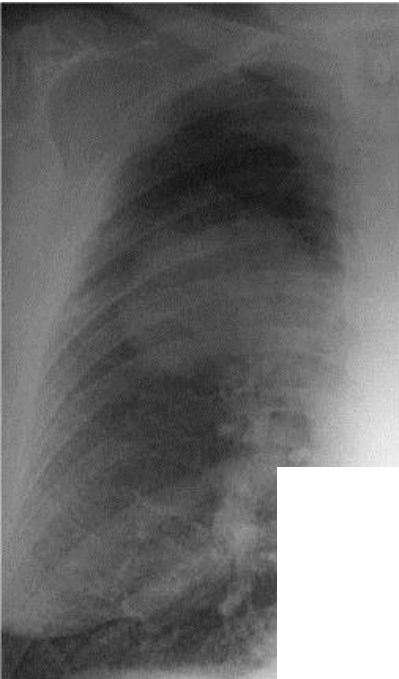
International Agency for Research on Cancer

World: Both sexes, all ages

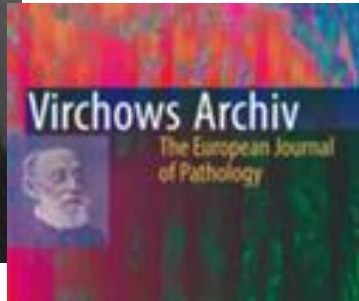
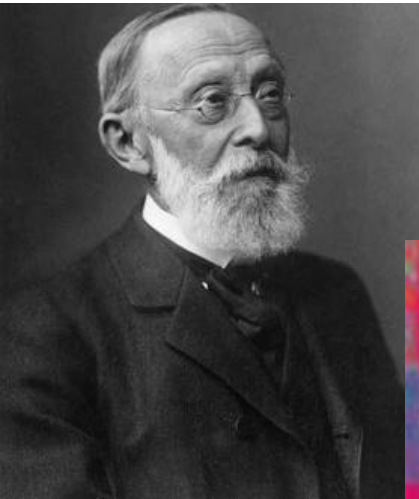


■ Incidence  
■ Mortality

## What is lung cancer ? The old perception



## Current definition of cancer

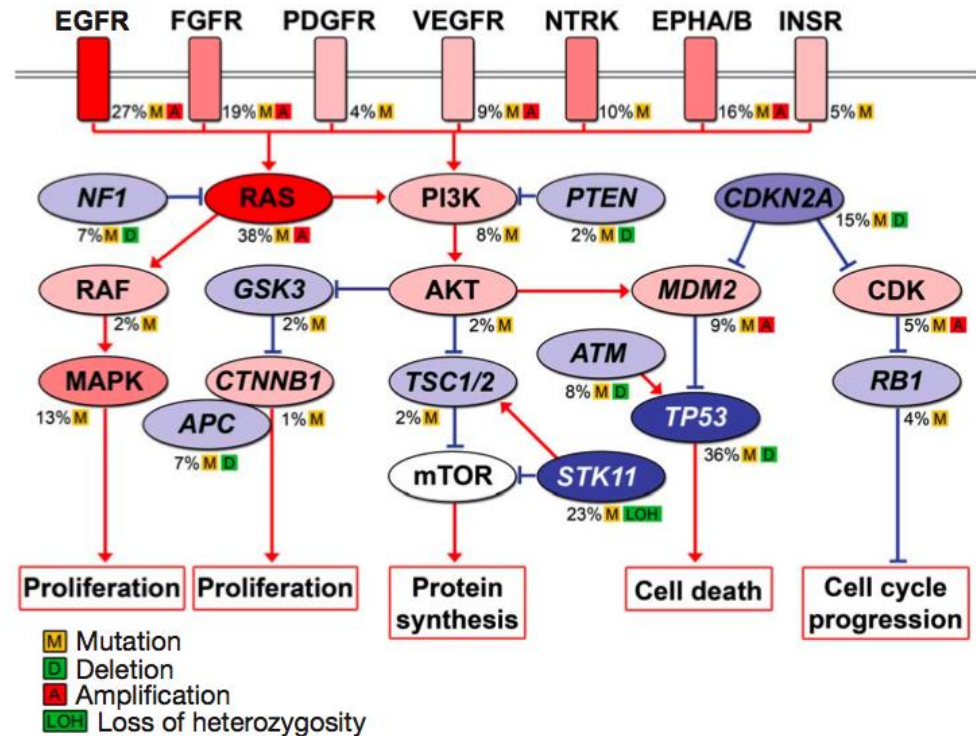


a tumor  
 an organ  
 a pathological sample

=

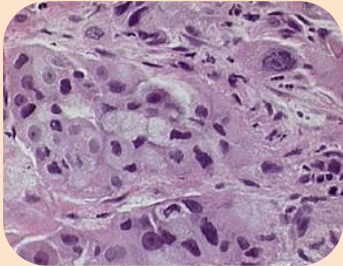
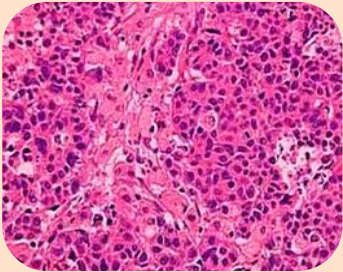
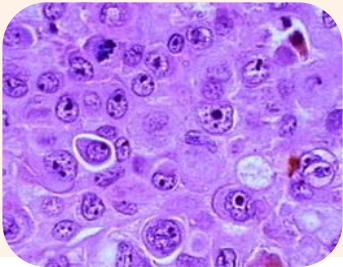
A definition from the XIXth century

Significantly mutated pathways in adenocarcinoma of the lung



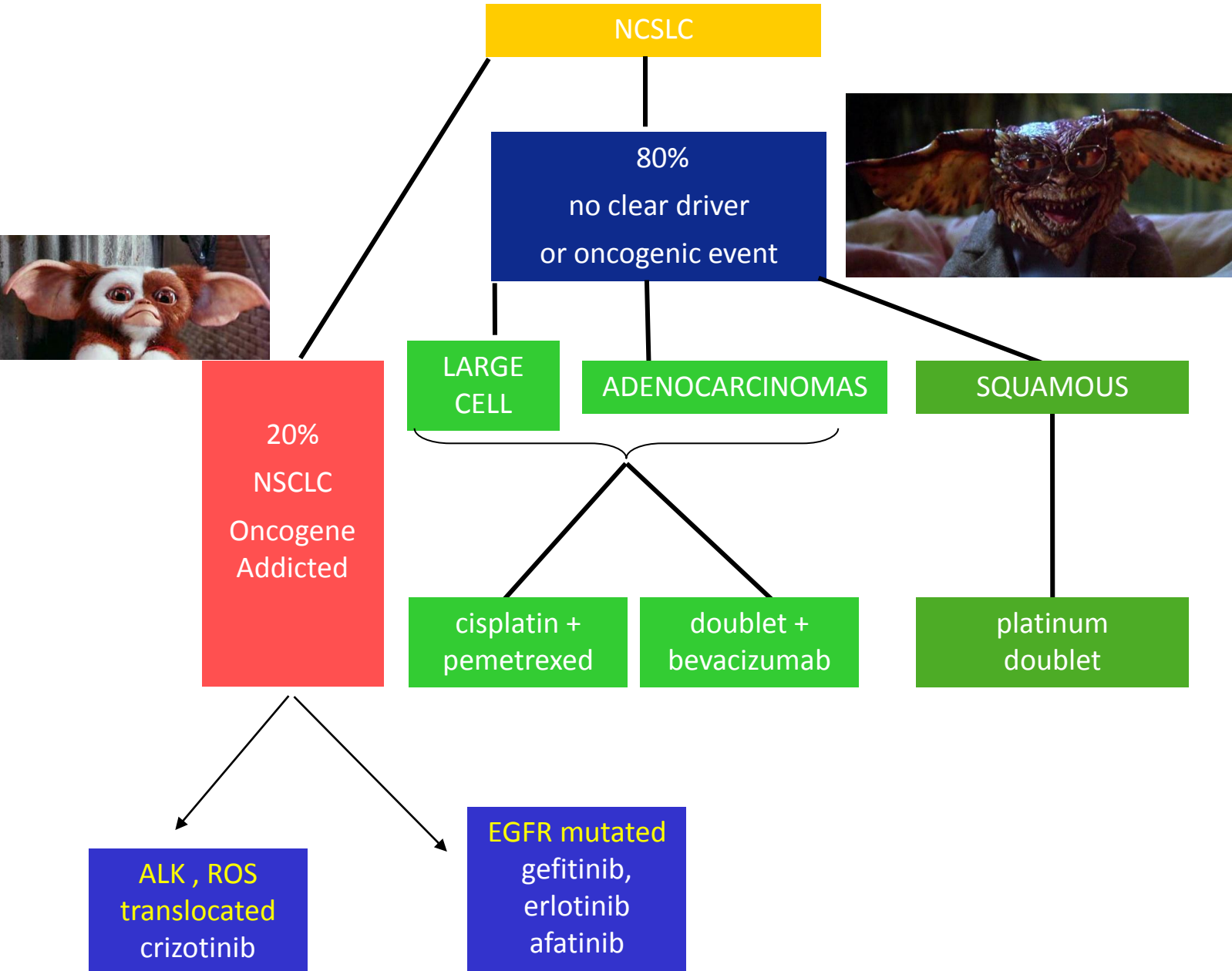


## In daily practice, histology remains the main classifier of NSCLC

Classification			Characteristics <sup>1</sup>
Non-squamous <sup>‡</sup>	<b>Adenocarcinoma</b> 30–50%* 		<ul style="list-style-type: none"> <li>• Malignant epithelial tumors with glandular differentiation</li> <li>• Subtypes are acinar, papillary, bronchoalveolar carcinoma (BAC), and solid adenocarcinoma with mucin production</li> <li>• Usually peripherally located</li> </ul>
	<b>Large cell carcinoma</b> 10%* 		<ul style="list-style-type: none"> <li>• Involves large cells (subtypes are giant cell, clear cell) with large nuclei</li> <li>• No evidence of squamous or glandular differentiation</li> <li>• Usually peripherally located</li> </ul>
Squamous	<b>Squamous cell carcinoma</b> 30% <sup>†</sup> 		<ul style="list-style-type: none"> <li>• Involves cells of the squamous epithelium</li> <li>• Usually centrally located</li> </ul>

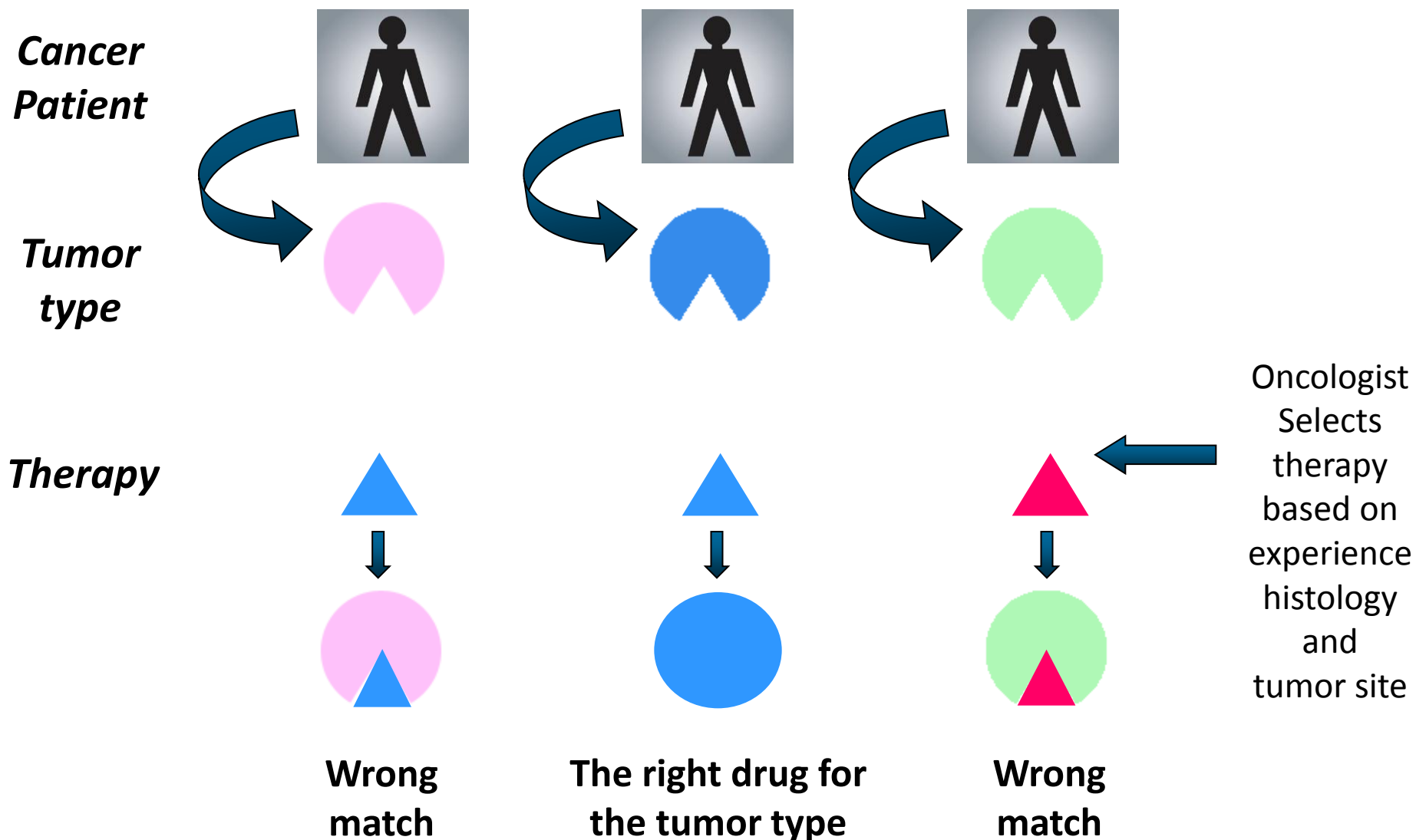
\*Image from [www.surgical-pathology.com](http://www.surgical-pathology.com); †Image from <http://www.lmp.ualberta.ca/resources/pathoimages/PC-S.htm>;

<sup>‡</sup>Other less common subtypes of non-squamous NSCLC include adenosquamous carcinoma and sarcomatoid carcinoma.<sup>3</sup>

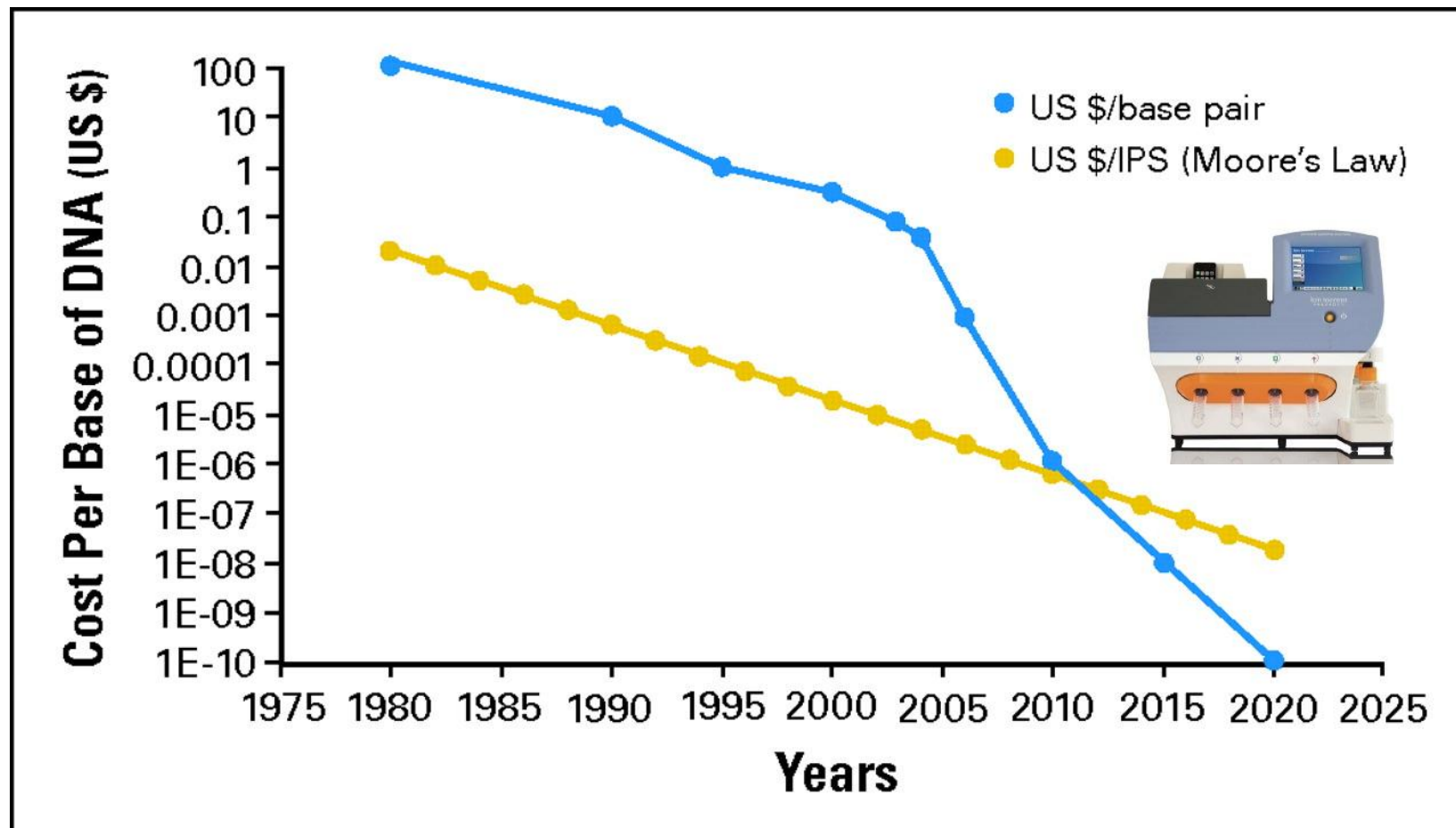




# Selecting the right therapy



**Driver-pathways will increase in number notably because of the reduced cost of sequencing**



MacConaill L E , Garraway L A JCO 2010;28:5219-5228

# Overview

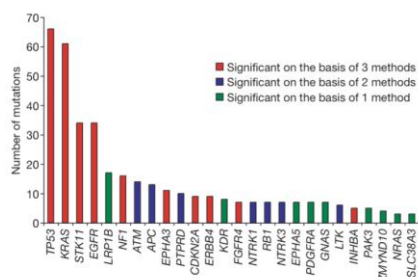
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# Many previous large-scale sequencing efforts in adenocarcinoma

Vol 455 23 October 2009 doi:10.1038/nature07423

## ARTICLES

### Somatic mutations affect key pathways in lung adenocarcinoma



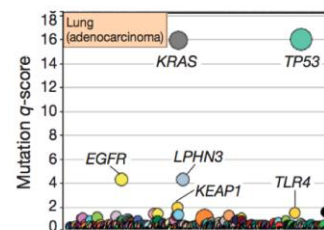
Ding et al 2008

623 genes in 188 Lung Adeno

## LETTERS

### Diverse somatic mutation patterns and pathway alterations in human cancers

Zhengyan Kan<sup>1,2</sup>, Bijay S. Jaiswal<sup>1</sup>, Jeremy Stinson<sup>1</sup>, Vasantharajan Janakiraman<sup>1</sup>, Deepali Bhatt<sup>1</sup>, Howard M. Stern<sup>1</sup>, Peng Yue<sup>1</sup>, Peter M. Haverly<sup>1</sup>, Richard Bourgon<sup>1</sup>, Jianbiao Zheng<sup>1</sup>, Martin Moonhead<sup>1</sup>, Subhra Choudhuri<sup>1</sup>, Lynn P. Tomsho<sup>1</sup>, Brock A. Peters<sup>1</sup>, Kanan Pujara<sup>1</sup>, Shaun Cordes<sup>1</sup>, David P. Davis<sup>1</sup>, Victoria E. H. Carlton<sup>1</sup>, Wenlin Yuan<sup>1</sup>, Li Li<sup>1</sup>, Weiwei Wang<sup>1</sup>, Charles Eigenbrodt<sup>1</sup>, Joshua S. Kaminker<sup>1</sup>, David A. Eberhard<sup>1</sup>, Paul Waring<sup>1</sup>, Stephan C. Schuster<sup>1</sup>, Zora Modrusan<sup>1</sup>, Zemin Zhang<sup>1</sup>, David Stokoe<sup>1</sup>, Frederic J. de Sauvage<sup>1</sup>, Malek Faham<sup>1</sup> & Somasekar Seshagiri<sup>1</sup>



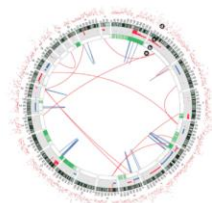
Kan et al 2010

1507 genes in 57 Lung Adeno

## LETTERS

### The mutation spectrum revealed by paired genome sequences from a lung cancer patient

William Lee<sup>1</sup>, Zhaozhi Jiang<sup>1</sup>, Jinfeng Liu<sup>1</sup>, Peter M. Haverly<sup>1</sup>, Yinghui Guan<sup>1</sup>, Jeremy Stinson<sup>2</sup>, Peng Yue<sup>1</sup>, Yan Zhang<sup>1</sup>, Krishna P. Pant<sup>1</sup>, Deepali Bhatt<sup>1</sup>, Connie Ha<sup>1</sup>, Stephanie Johnson<sup>1</sup>, Michael I. Kennerly<sup>1</sup>, Sankar Mohan<sup>1</sup>, Igor Nazarenko<sup>1</sup>, Colin Watanabe<sup>1</sup>, Andrew B. Sparks<sup>1</sup>, David S. Shames<sup>1</sup>, Robert Gentleman<sup>1</sup>, Frederic J. de Sauvage<sup>1</sup>, Howard Stern<sup>1</sup>, Ajay Pandita<sup>1</sup>, Dennis G. Ballinger<sup>1</sup>, Radoje Drmanac<sup>1</sup>, Zora Modrusan<sup>1</sup>, Somasekar Seshagiri<sup>1</sup> & Zemin Zhang<sup>1</sup>

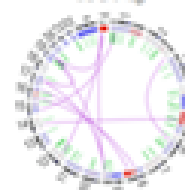


Lee et al 2010

WGS of a single Lung Adeno T-N pair

LUAD-801381

UCAF1 54H  
KEAP1 196L  
TSG Neg



SIK2 In-frame dup  
 LRP1B In-frame dup

LUAD-B00934

Onc Neg  
TSG Neg



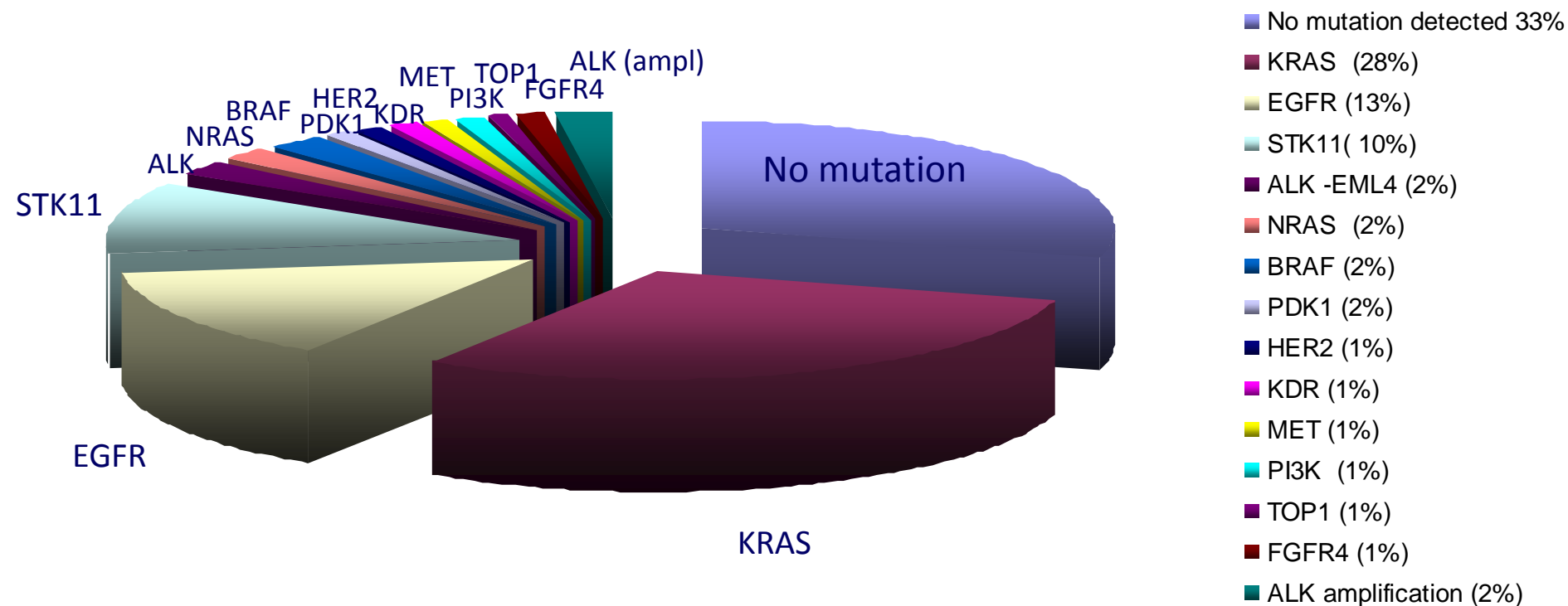
SSBP2-NEU54 fusion  
 PRKCA In-frame dup

Ju et al 2011

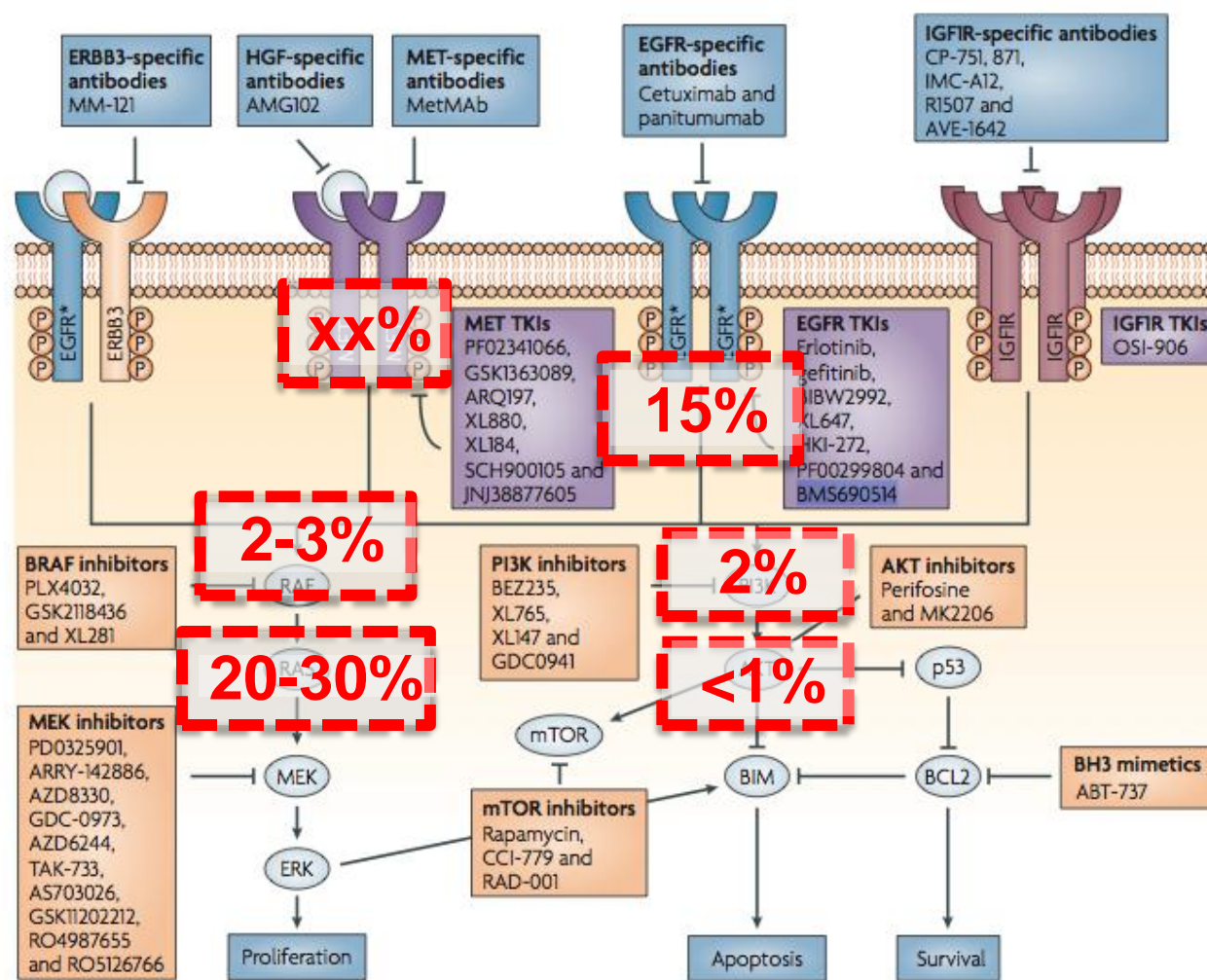
WGS of a single Lung Adeno T-N pair

# Incidence of driver mutations in adenocarcinoma

**Mutations found in 67% (IGR experience)**

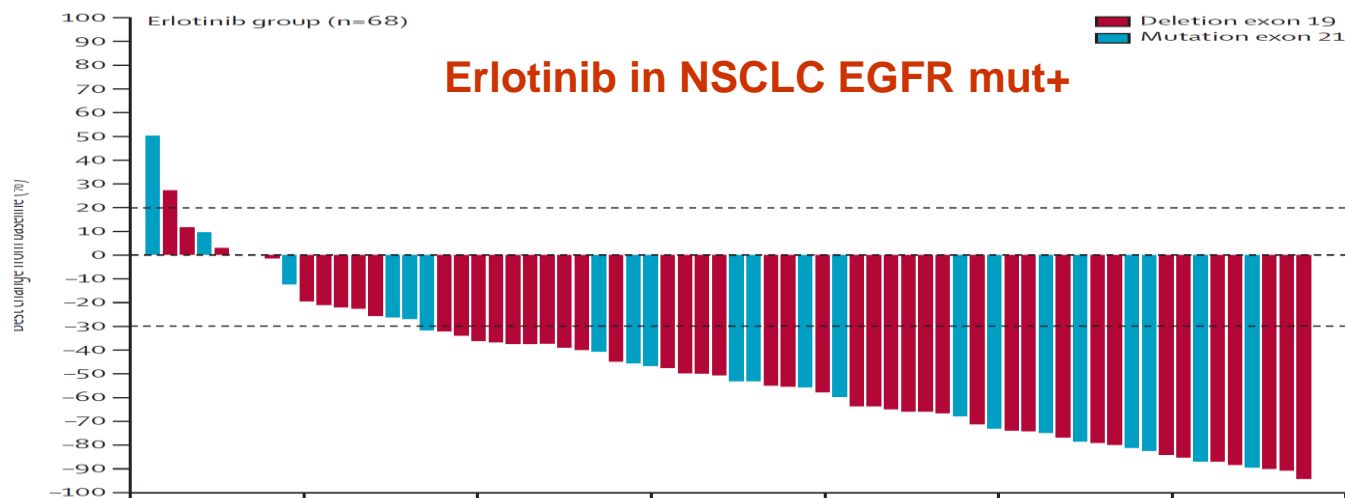


## The “targeted therapome” in lung adenocarcinoma



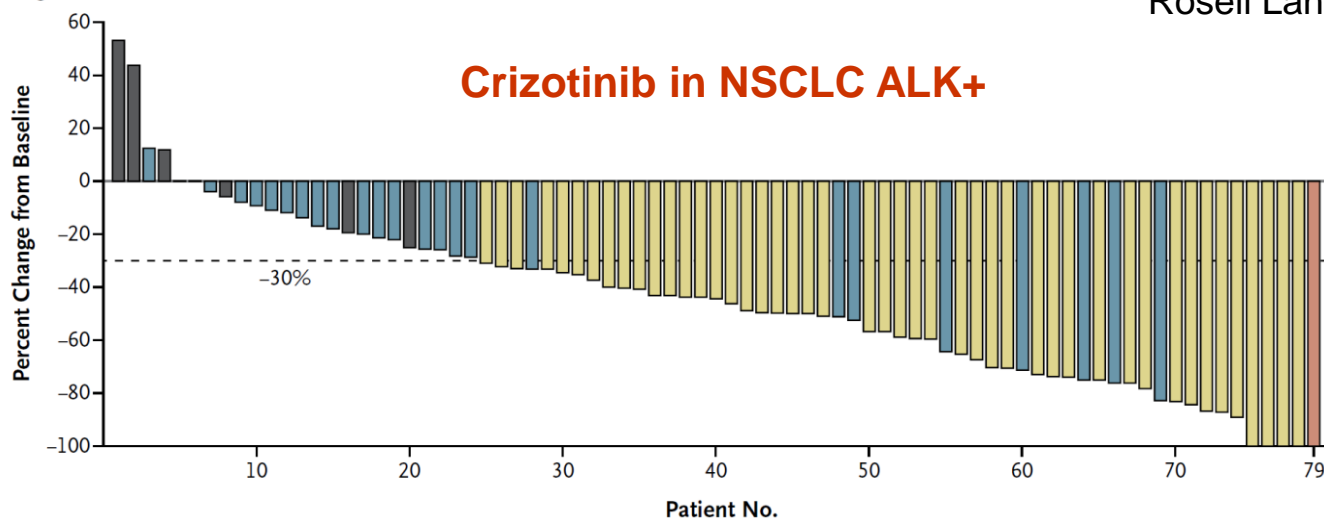


# Actionable alterations leading to clinical benefit



Percent Change in Tumor Burden

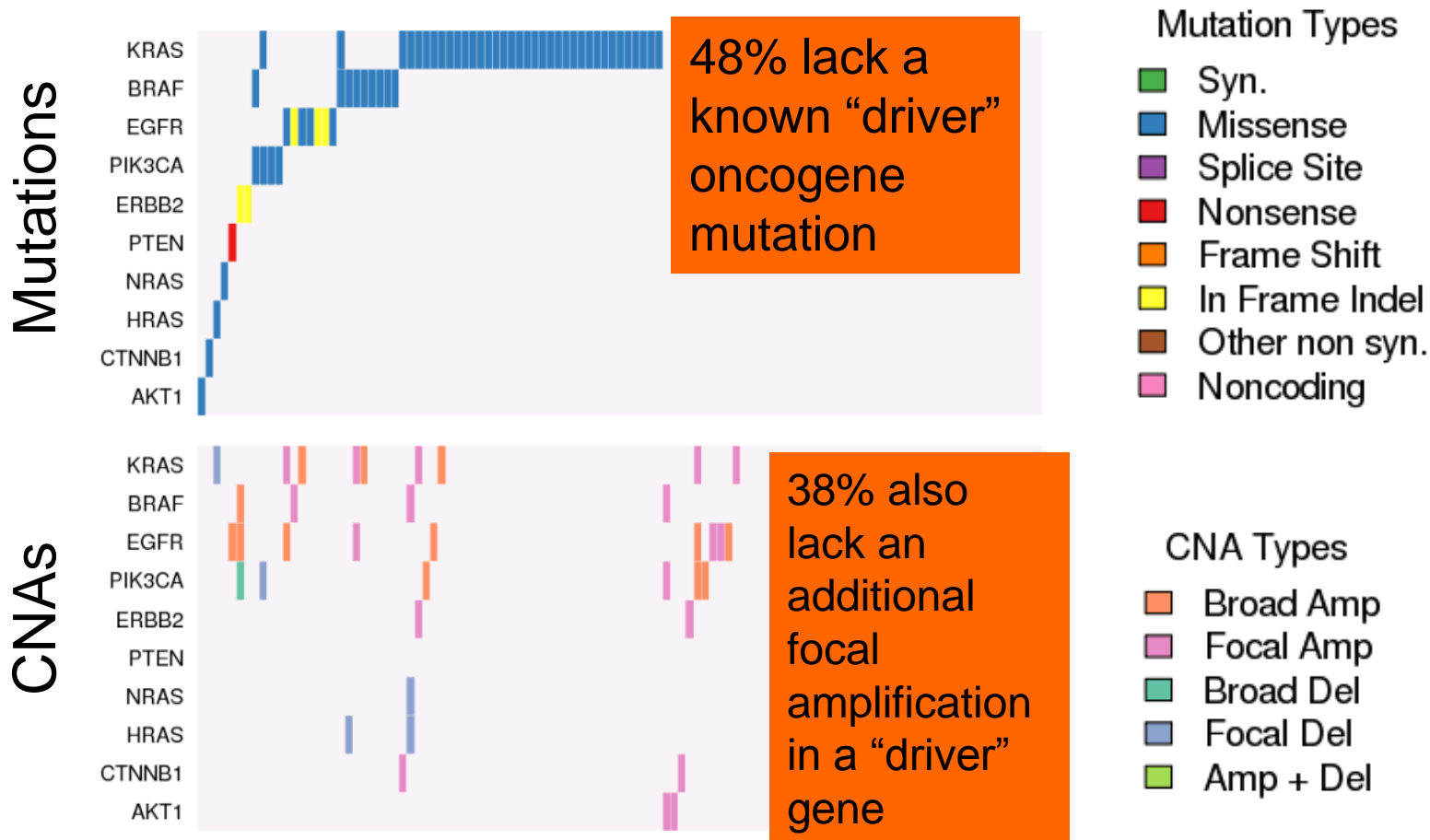
Rosell Lancet Oncol 12



Kwak NEJM 10

## Missing key driver oncogenes in lung adenocarcinoma

### Proliferation Drivers



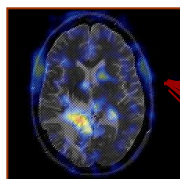
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# The Cancer Genome Atlas (TCGA): Complete cancer genome description

## 25 forms of cancer

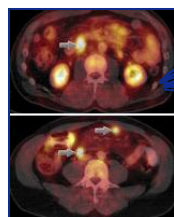
glioblastoma multiforme  
(brain)



squamous carcinoma  
(lung)



serous  
cystadenocarcinoma  
(ovarian)



Etc. Etc. Etc.

Biospecimen Core  
Resource with more  
than 150 Tissue Source  
Sites

6 Cancer Genomic  
Characterization  
Centers

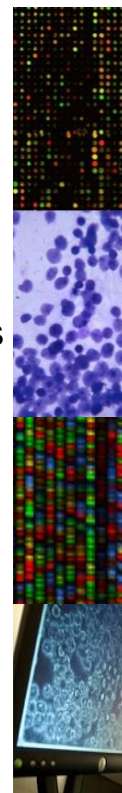
3 Genome  
Sequencing  
Centers

7 Genome Data  
Analysis Centers

Data Coordinating  
Center

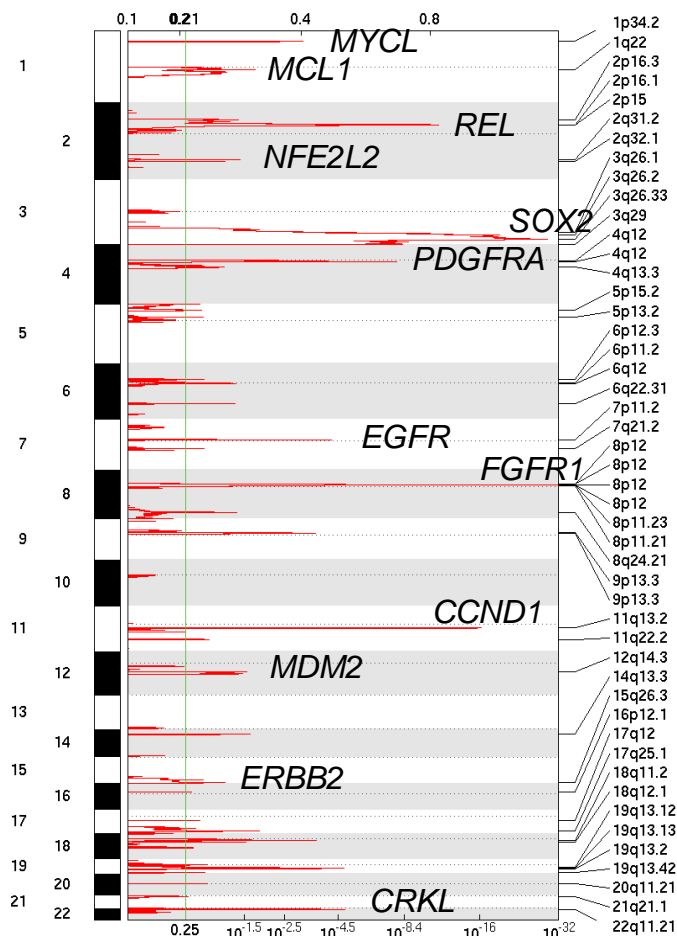
## Multiple data types

- Clinical diagnosis
- Treatment history
- Histologic diagnosis
- Pathologic report/images
- Tissue anatomic site
- Surgical history
- Gene expression/RNA sequence
- Chromosomal copy number
- Loss of heterozygosity
- Methylation patterns
- miRNA expression
- DNA sequence
- RPPA (protein)
- Subset for Mass Spec

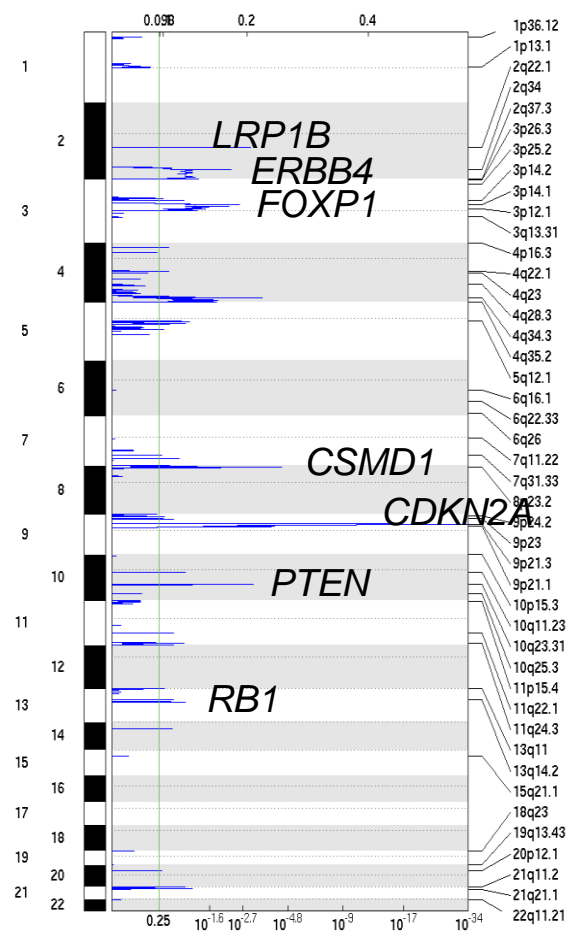


# Focal copy number alterations in squamous cell lung carcinoma

## Amplification

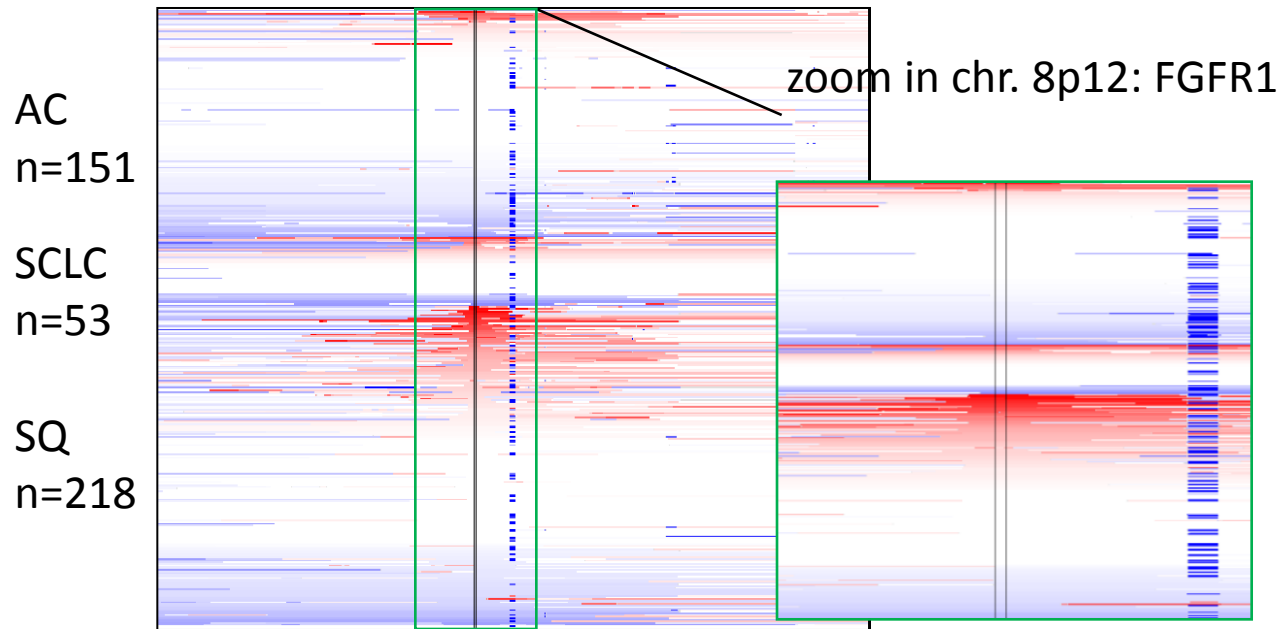


## Deletion

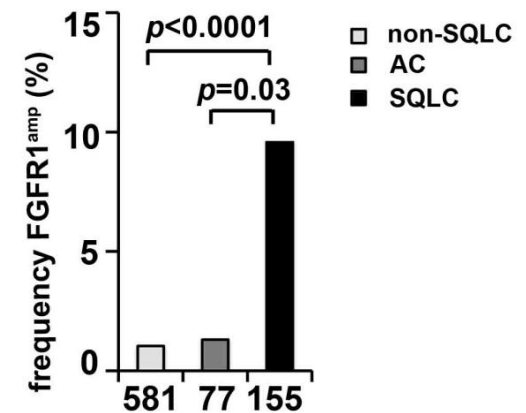
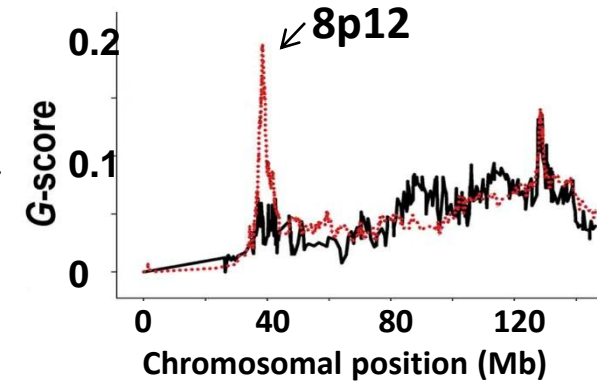


## FGFR1 as a relevant target in squamous cell carcinoma

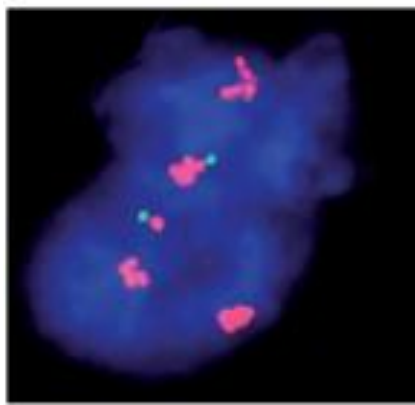
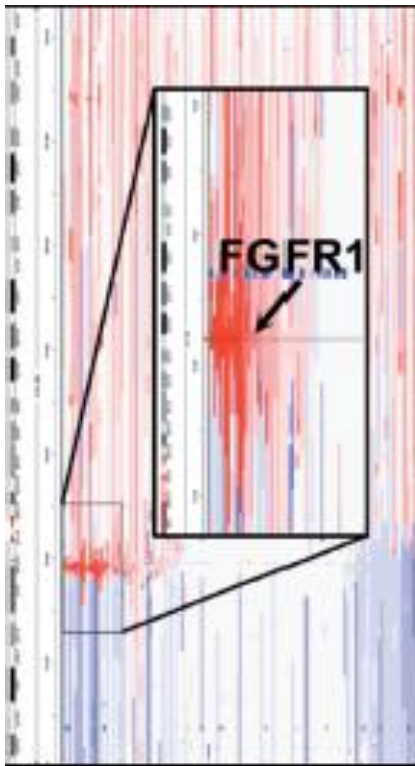
zoom in chromosome 8



The Clinical Lung Cancer Genome Project





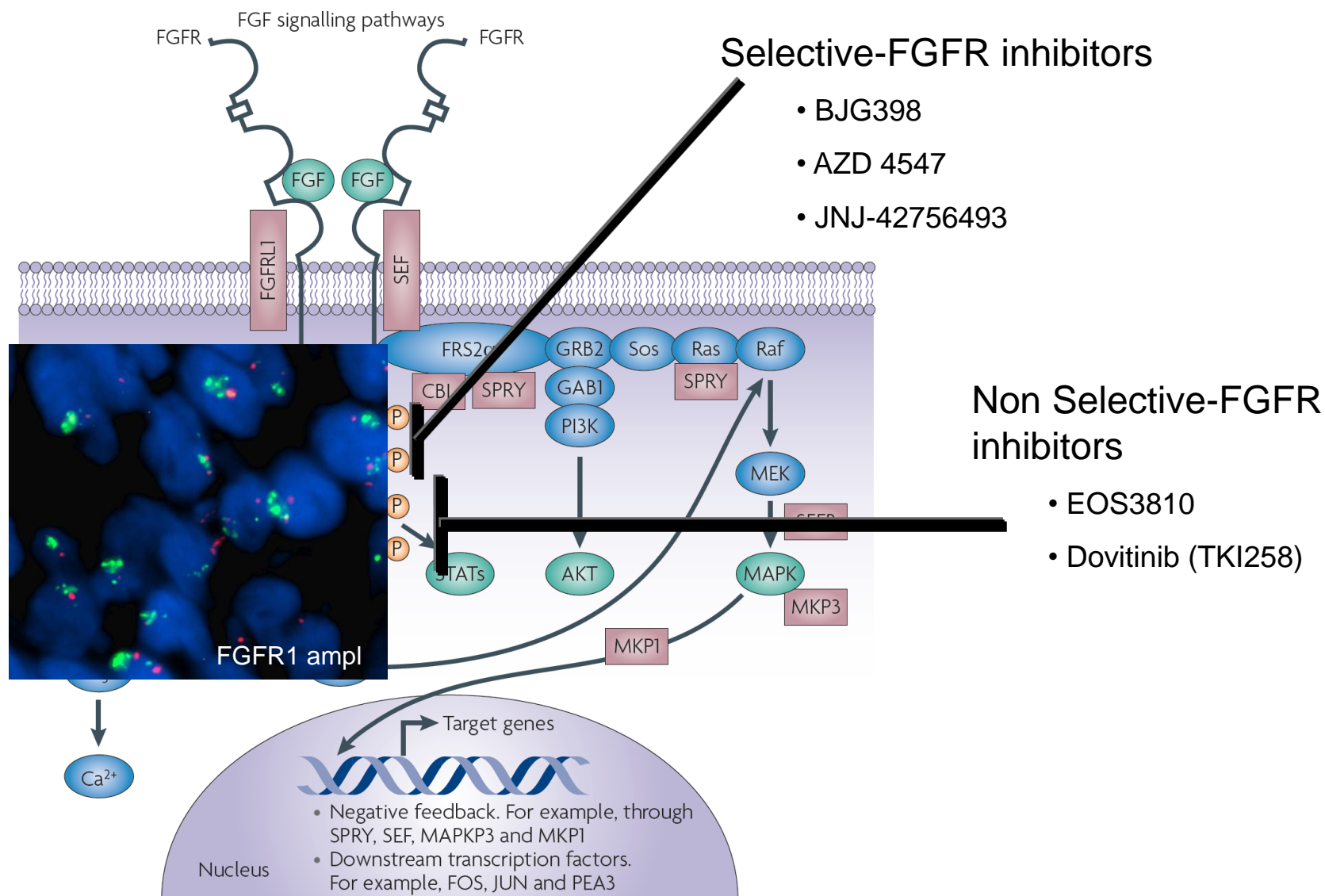


## FGR1 amplification

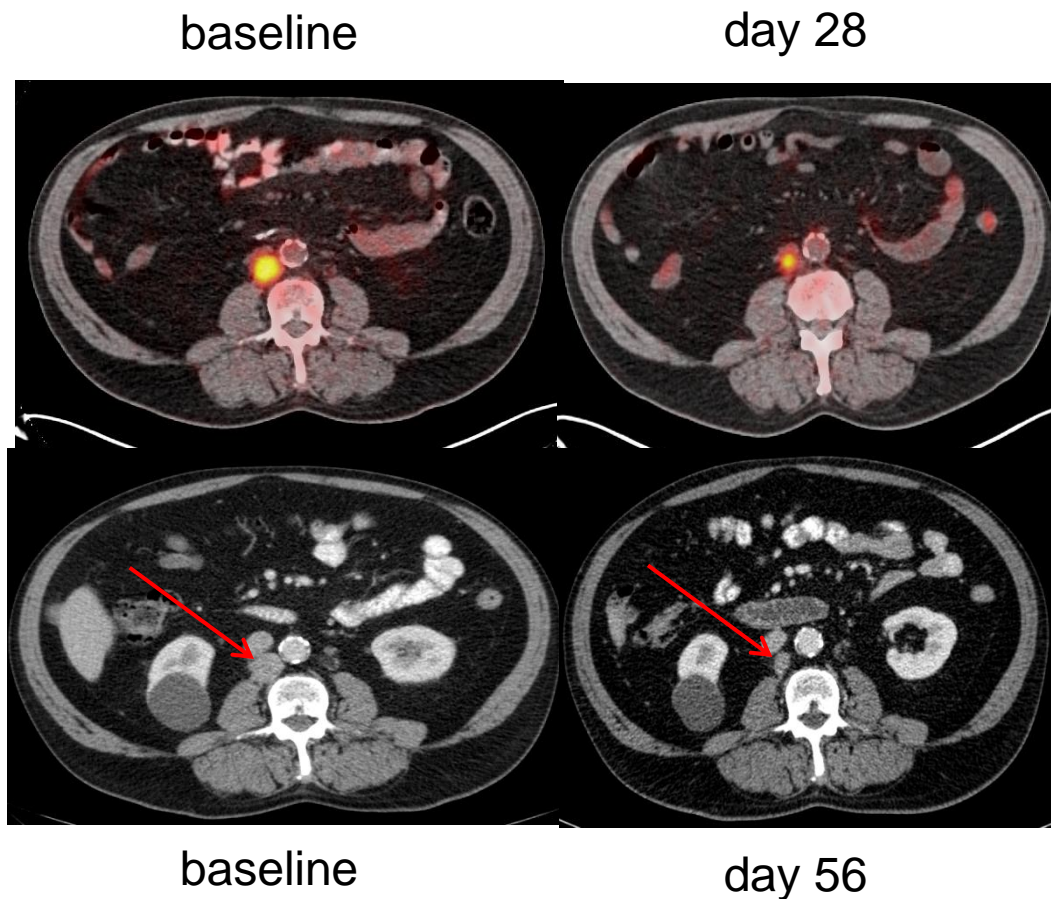
- 10% of SCC by CGH
- 20% of SCC by FISH (high levels > 8 copies)
- specific cell lines with FGR1 amplification sensitive to PD170374

The Clinical Lung Cancer Genome Project

## Targeting FGFR family

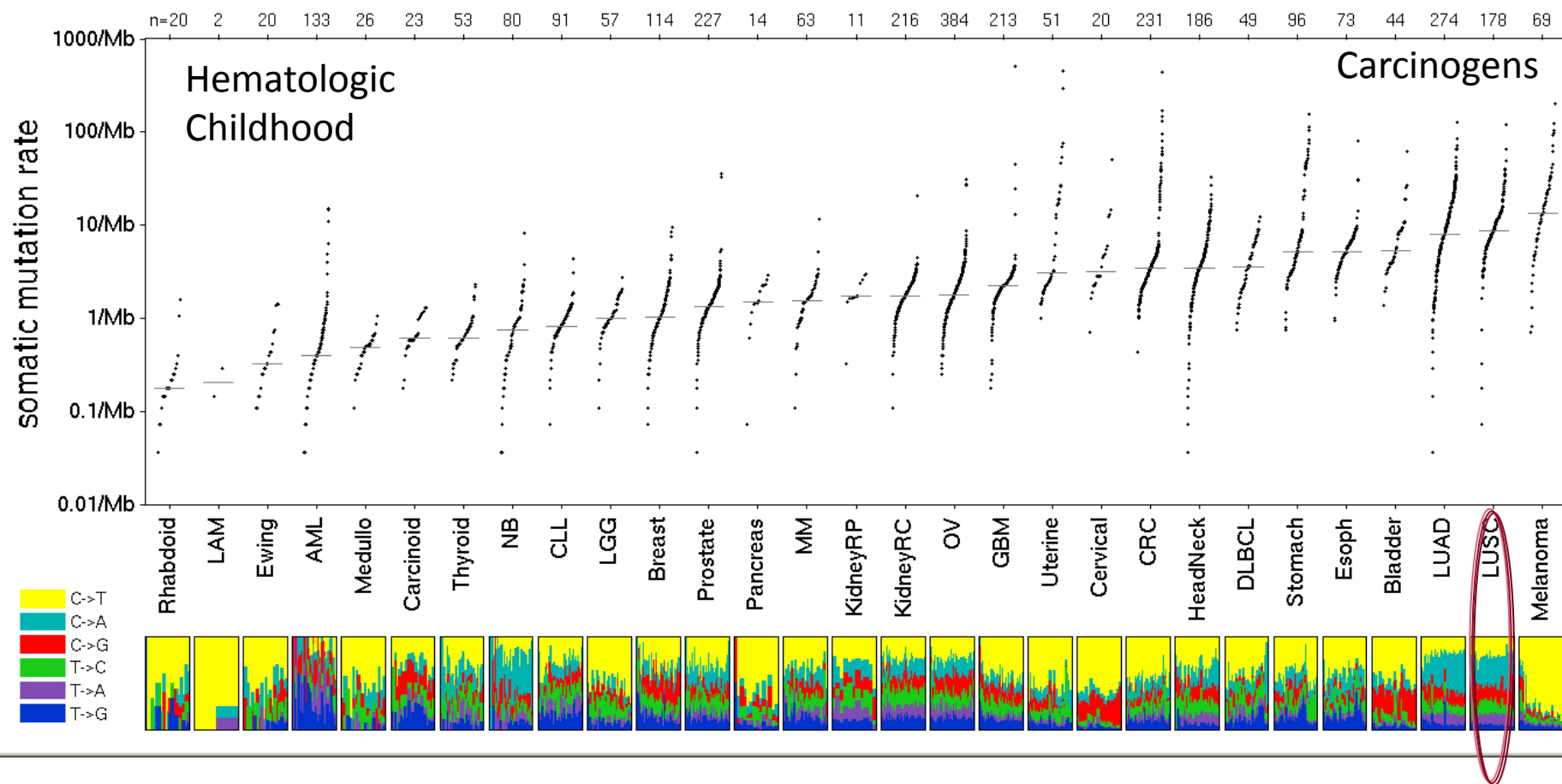


## Lung SCC at 100 mg BJG398: PR

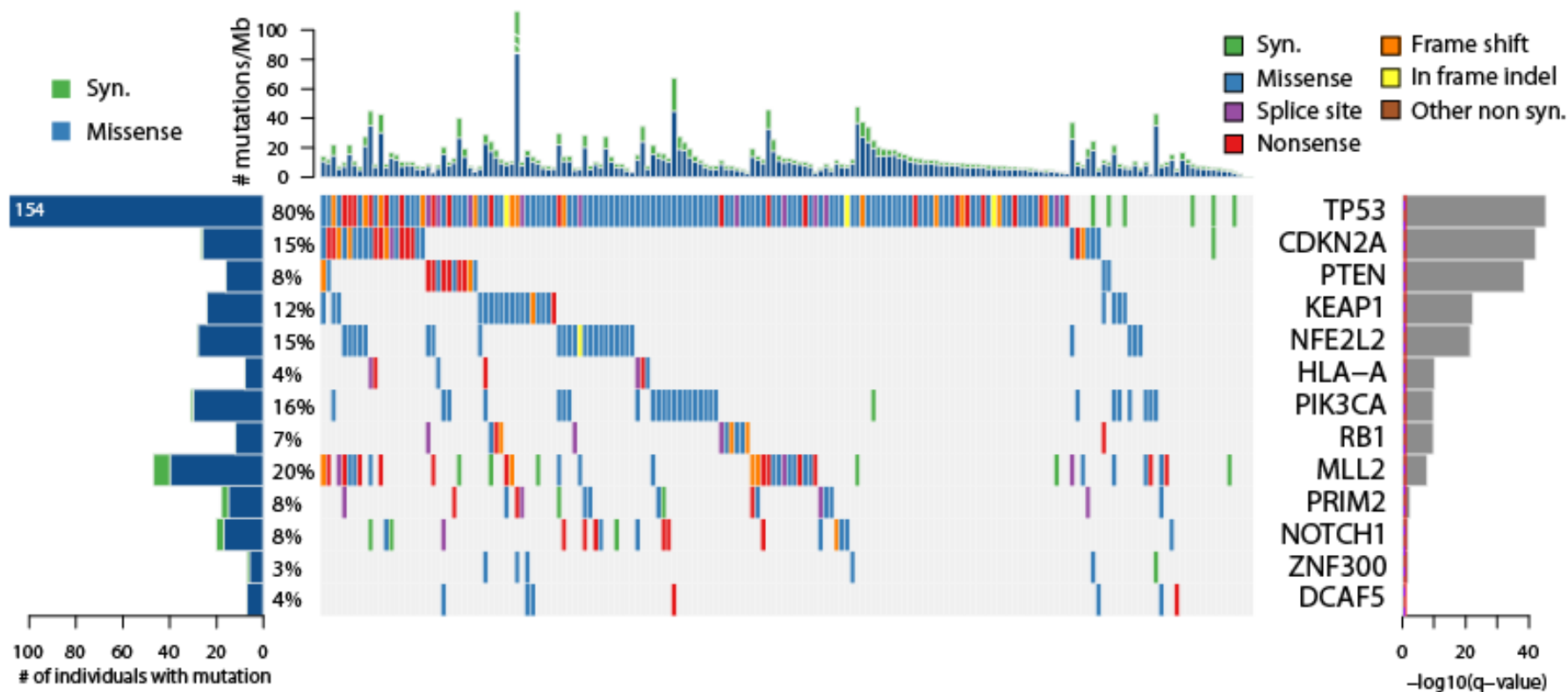


- Confirmed PR at D56 – patient presently in 7<sup>th</sup> cycle of treatment

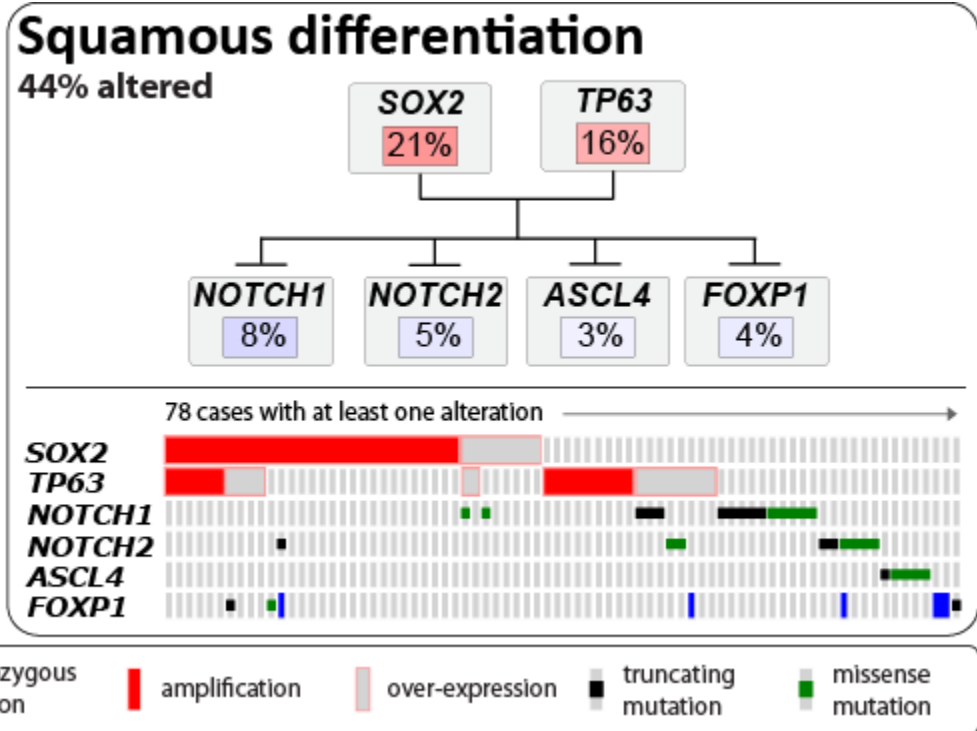
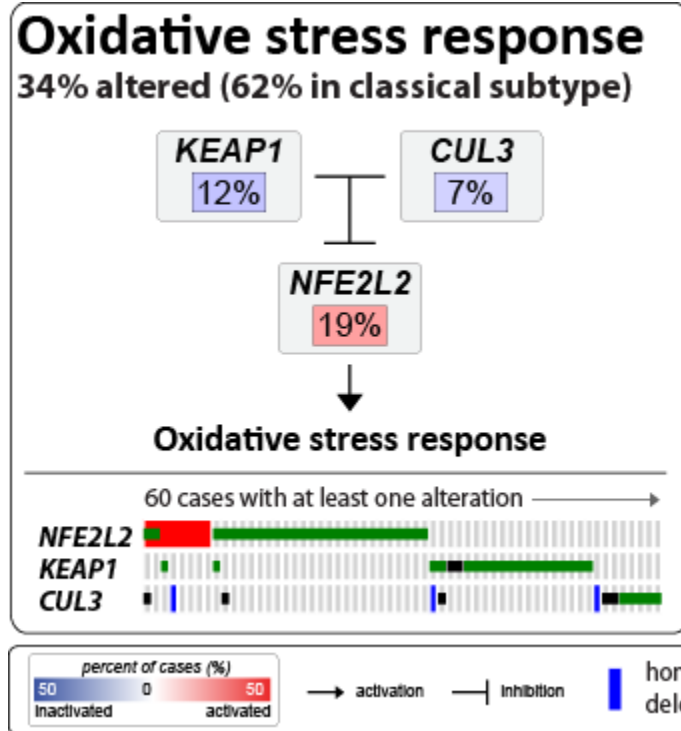
## SCC has a very high rate of somatic mutations



## Top mutated genes in SCC



# Oxidative response and differentiation pathway alterations in lung SCC

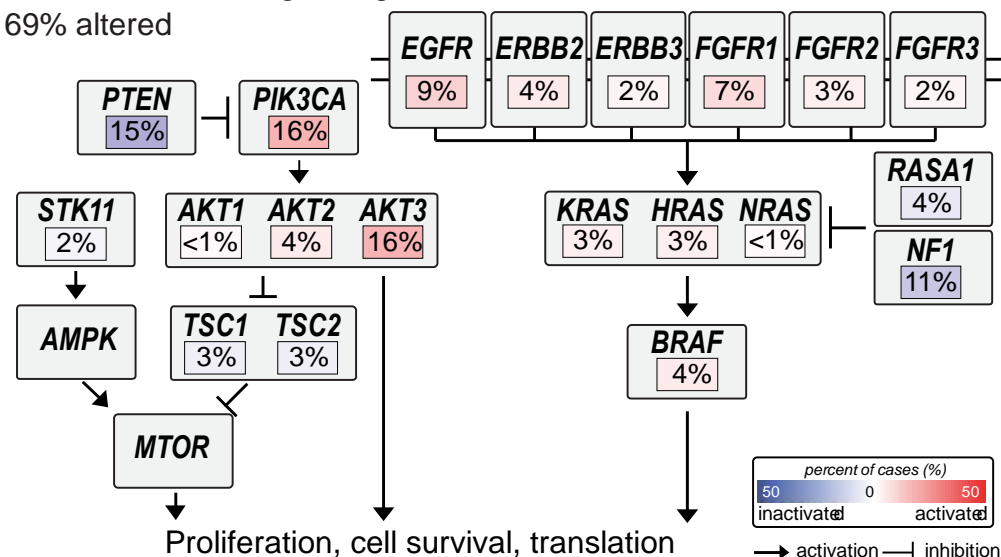




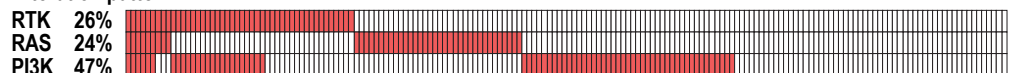
# Therapeutic targets in squamous cell lung carcinomas, defined by TCGA

PI3K/RTK/RAS signaling

69% altered



Alteration pattern

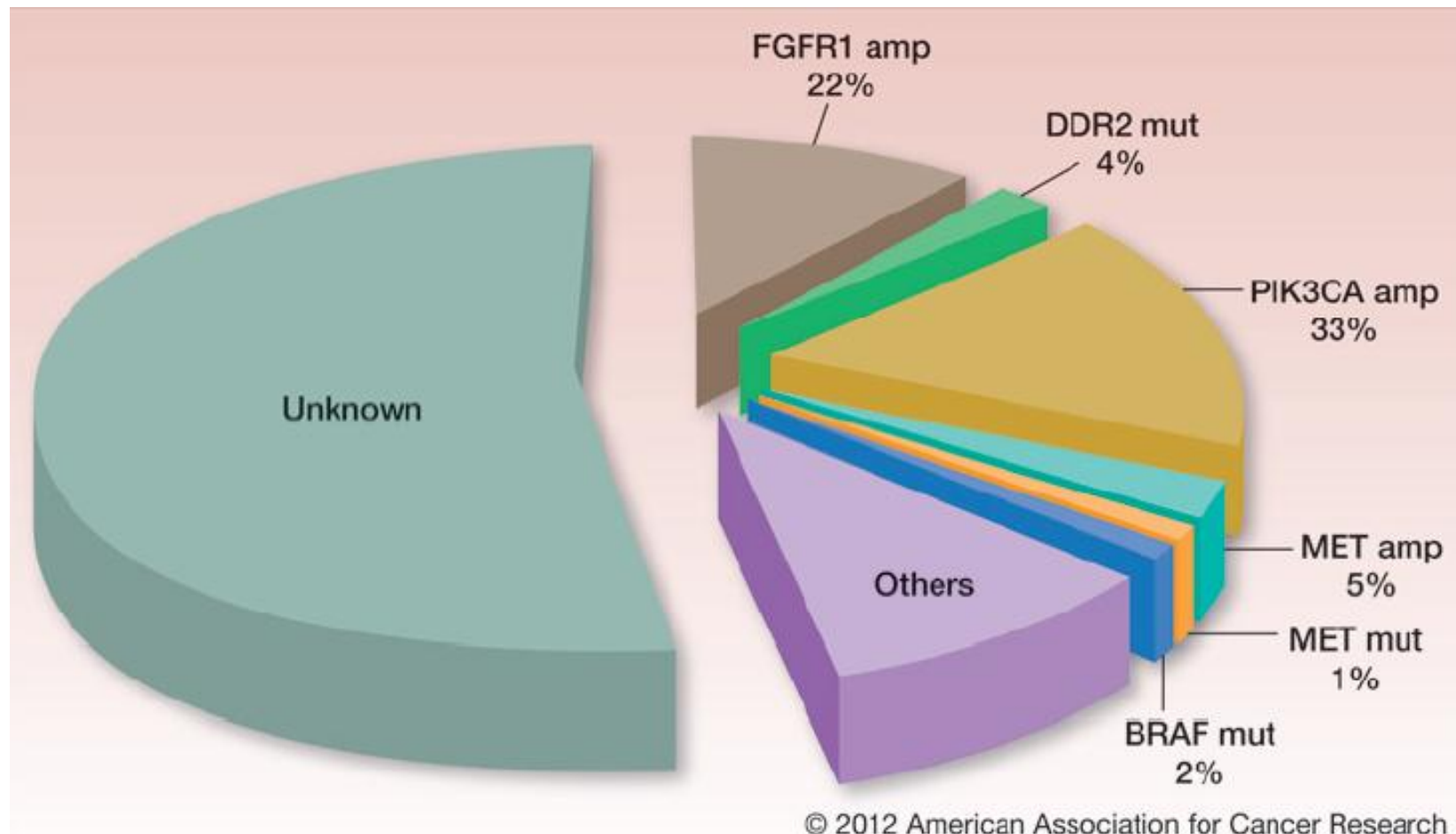


40 to 60% of lung SCCs have a possible therapeutic target—more if we include *CDKN2A* alterations—in a disease with no targeted therapies today

Targets will need to be validated  
In the clinical setting

FGFR1/2, PIK3CA and DDR2  
inhibitor trials are ongoing

## Frequencies of potentially actionable/targetable genetic abnormalities present in SCC of the lung



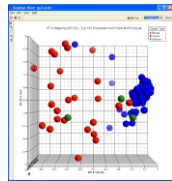
# Lung Cancer Patient in the near future

Lung nodule/metastases

Tumor Biopsy/ blood

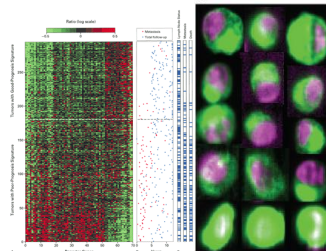
MOLECULAR PORTRAIT

*Diagnostic*



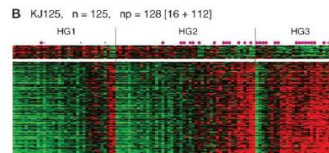
Cancer? Yes/No

*Prognosis*



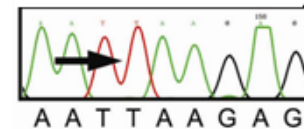
Need for treatment ?

*Chemotherapy sensitivity*



Which treatment and when ?

*Targeted therapy sensitivity*



*New target*

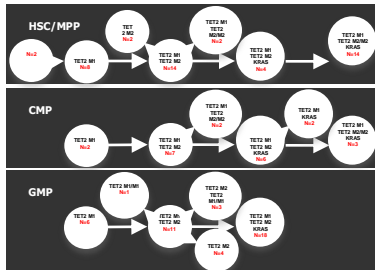
ALK  
 PI3K  
 FGFR1  
 AKT  
 Other  
 Pathways

...

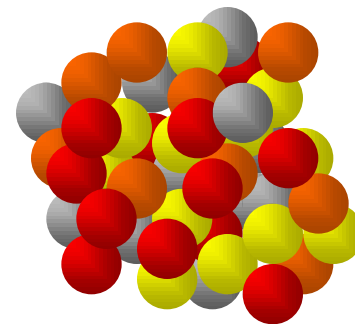
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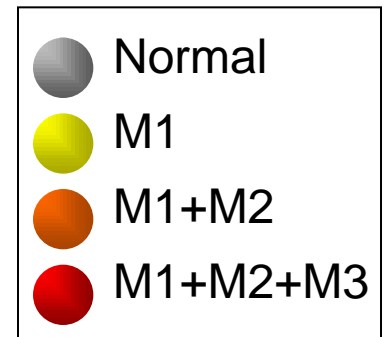
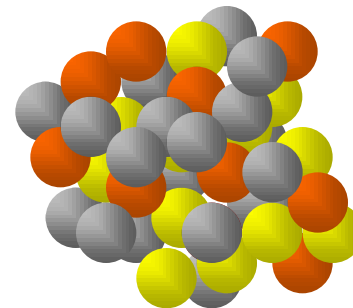
# Individual tumor heterogeneity: a limitation to MTA

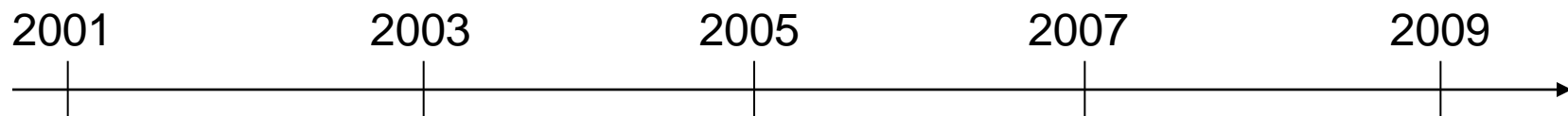


Clone architecture  
in NSCLC



M3-targeting drug



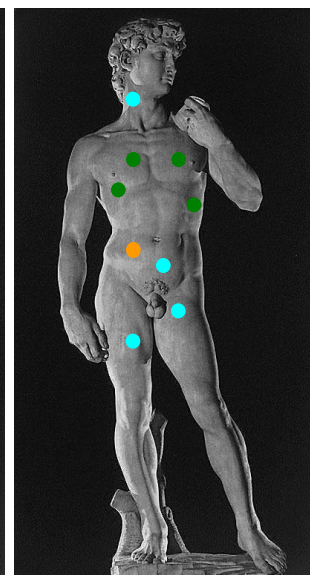
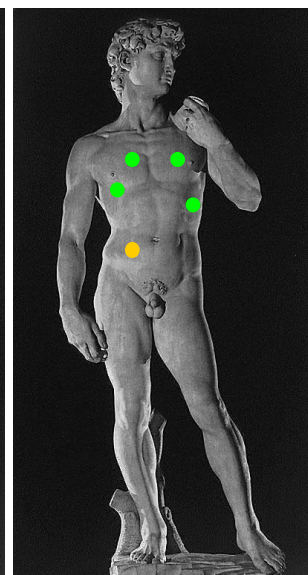
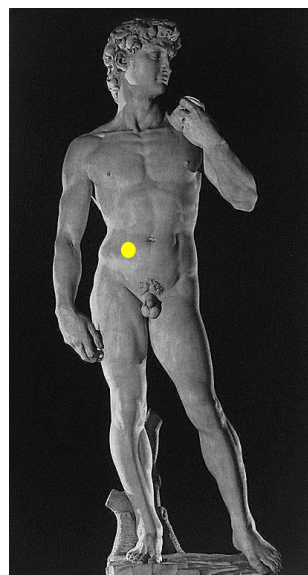
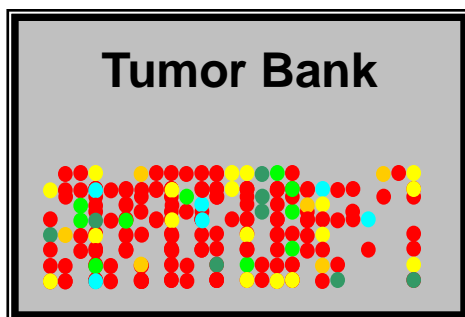
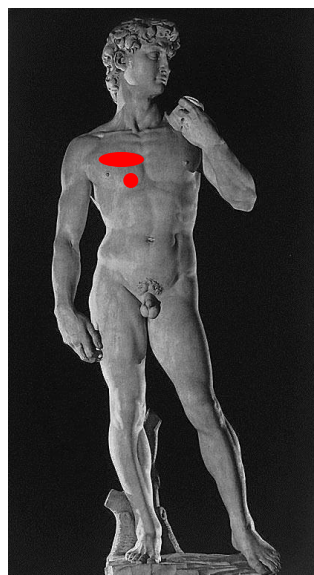


Surgery T1N1

Adrenal gland +

Lung +

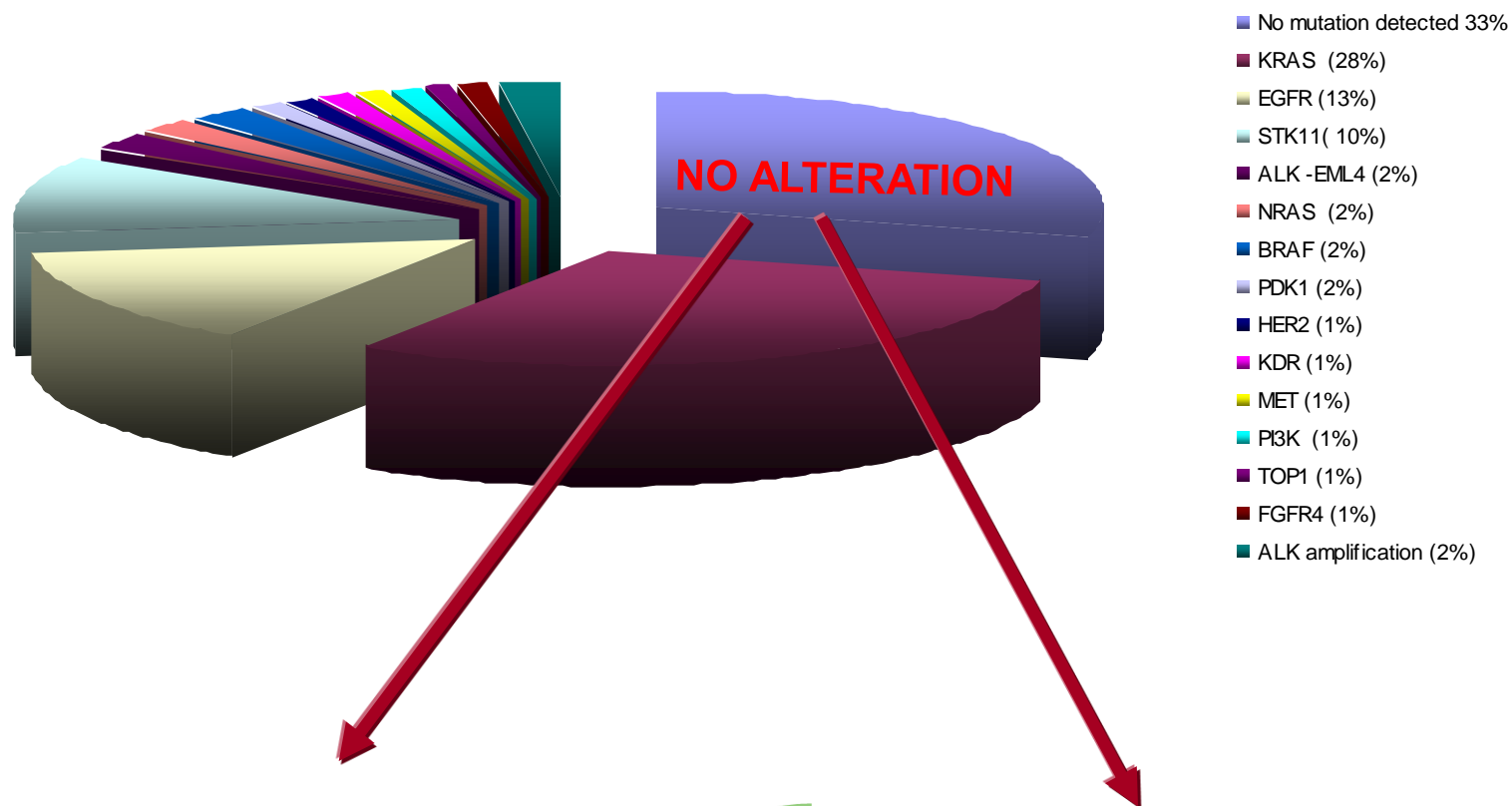
Bone +





Whole tumor	<i><b>Tissue</b></i>	Adrenal gland biopsy	-	-
Vinorelbine cisplatinum	<i><b>Treatment</b></i>	Taxol Carbo bevacizumab	Pemetrexed	Erlotinib



## How de we move forward for patients with unidentified alterations ???

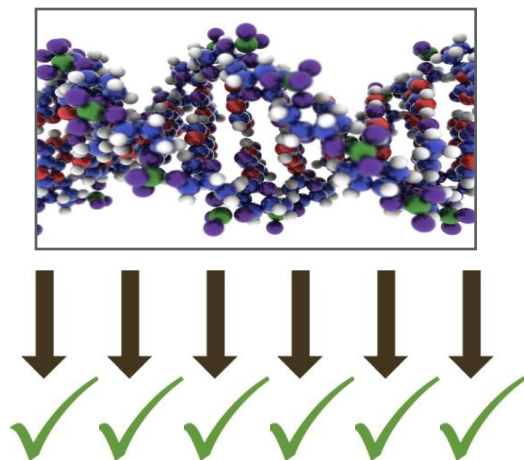



 Optimize the use of CT and XRT  
 Better understand DNA repair


 Active immunotherapies  
 Predictive biomarkers

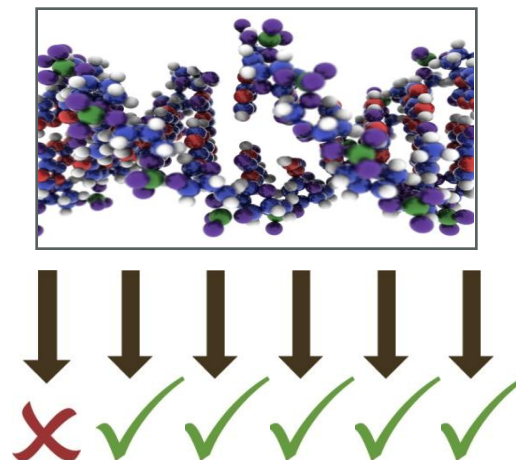
# DNA Repair Pathways Are Critical in Cancer

Normal cells



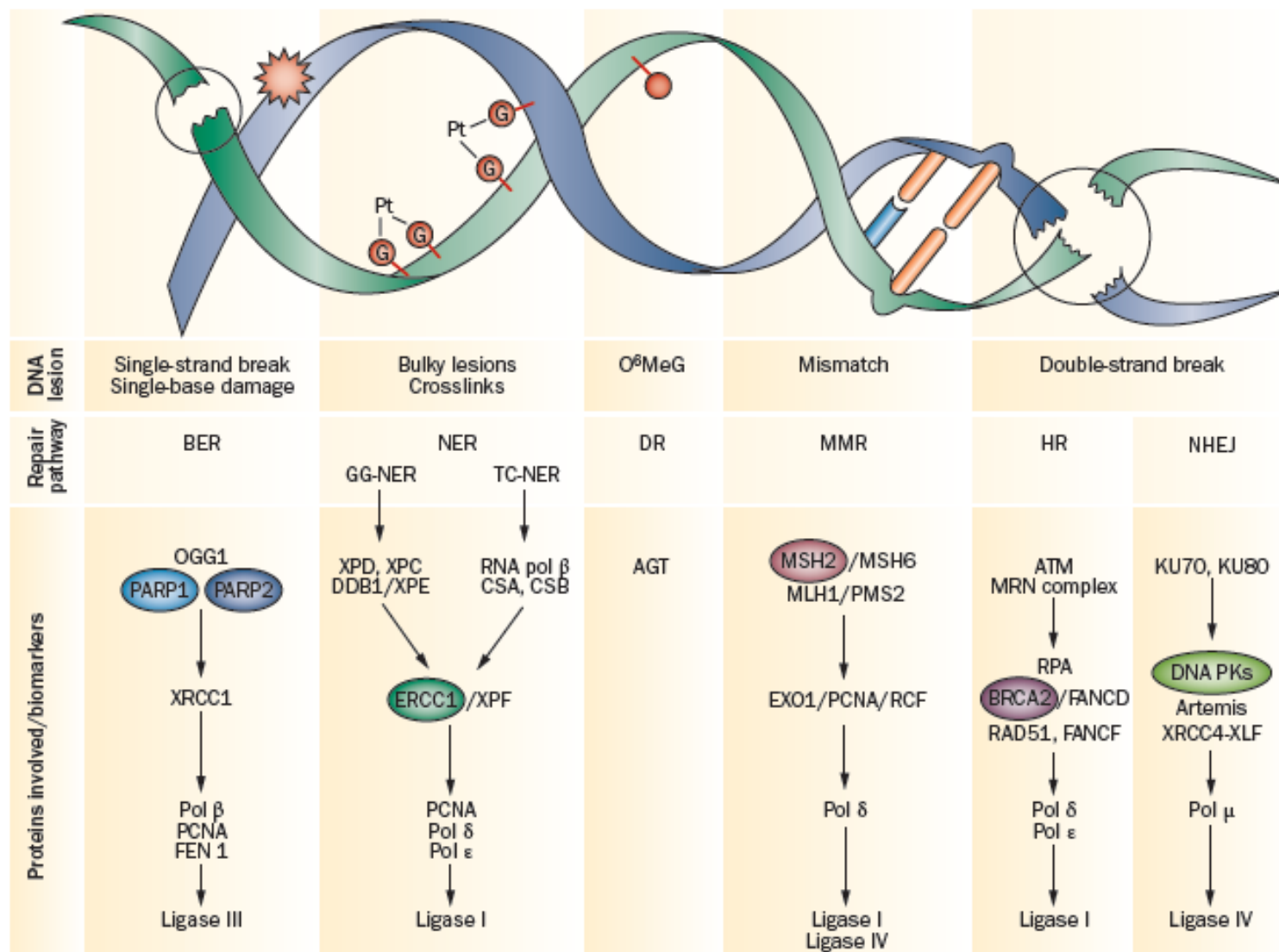
Six normal DNA repair pathways

Cancer cells

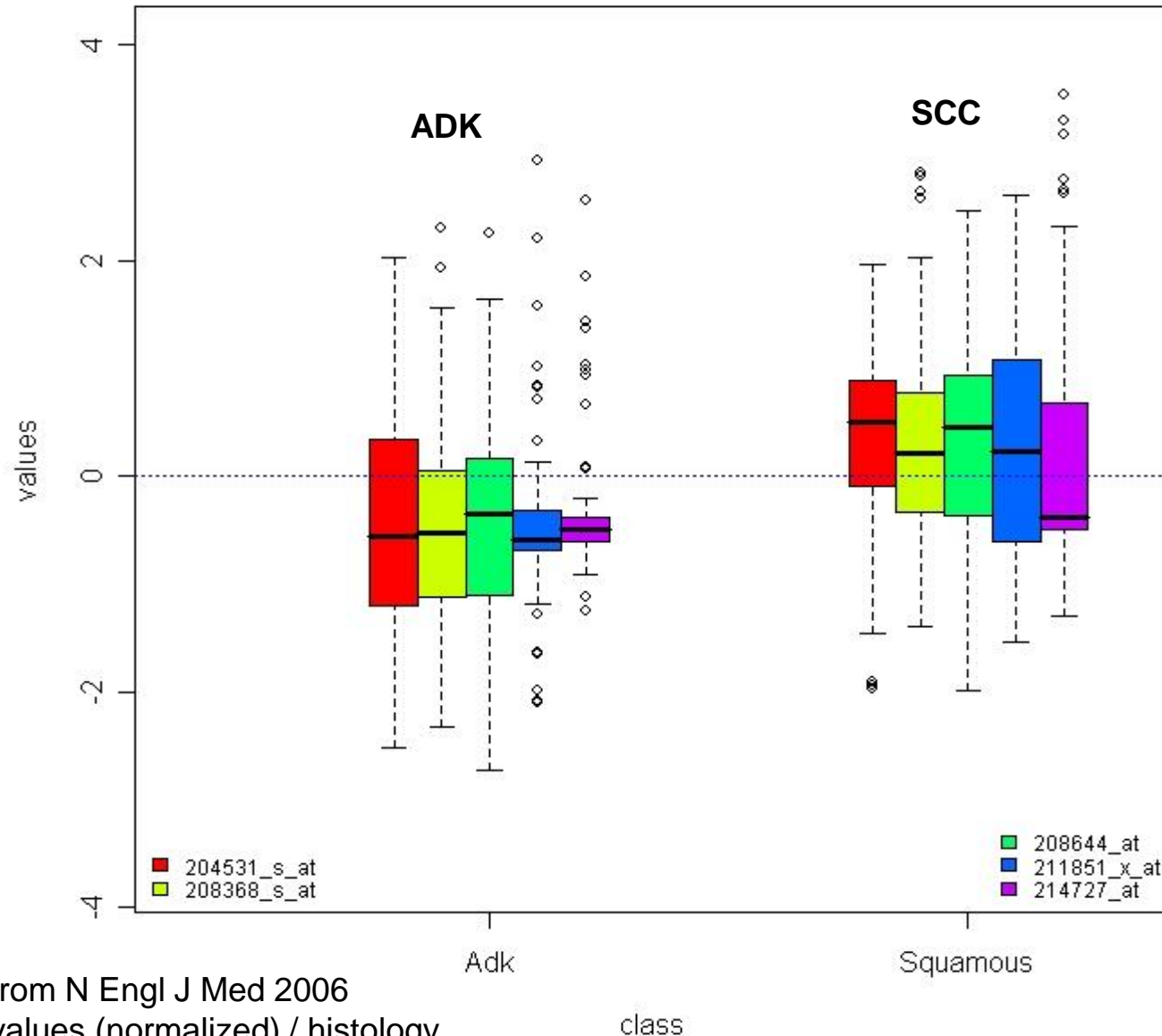


The specific pathway changes determine the best course of chemotherapy and radiation (personalized medicine)

# DNA repair pathways



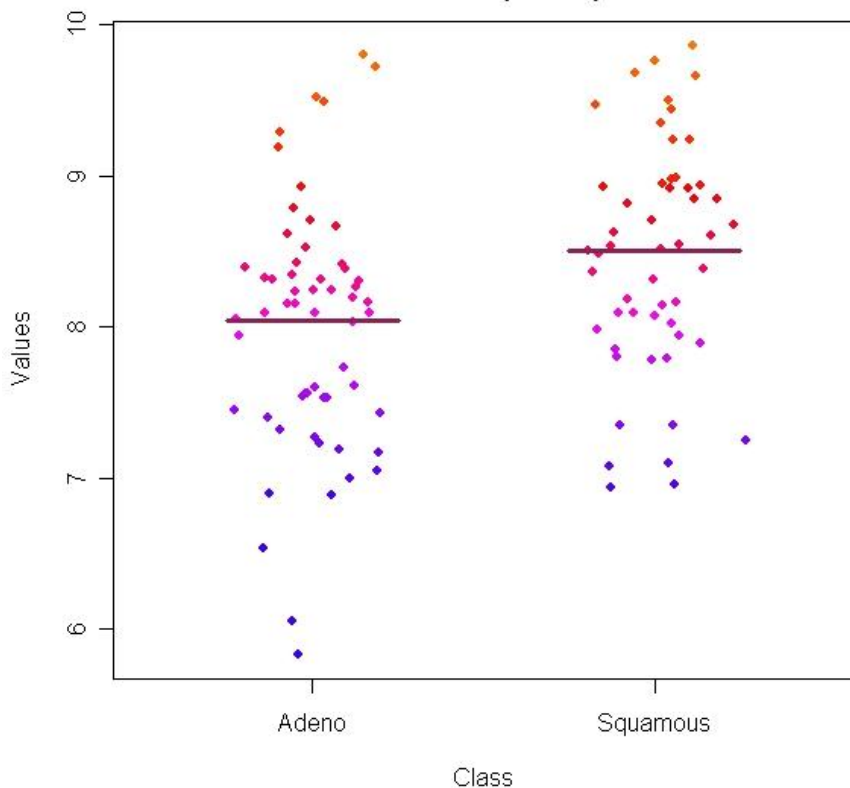
# Adenocarcinomas express low levels of PARP1 and BRCA1/2 compared to squamous histology



208644\_at = Parp1  
 204531\_s\_at = BRCA1  
 211851\_x\_at = BRCA1  
 208368\_s\_at = BRCA2  
 214727\_at = BRCA2

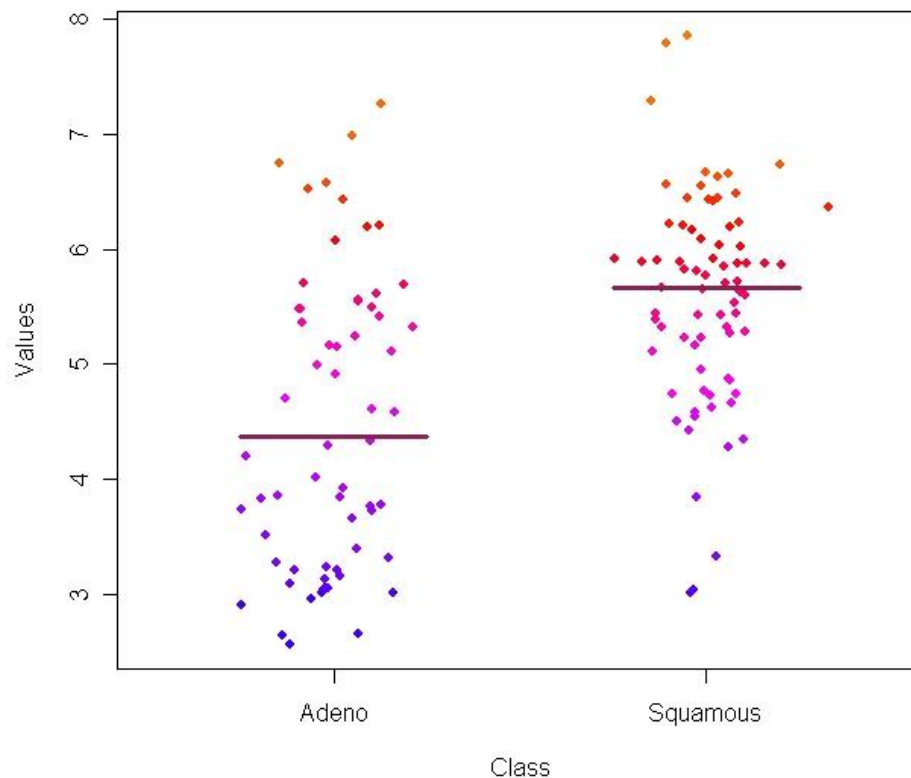
## CHEK1 expression according to histotype

**CHEK1 according to tumor type**  
**Bild data (n=111)**

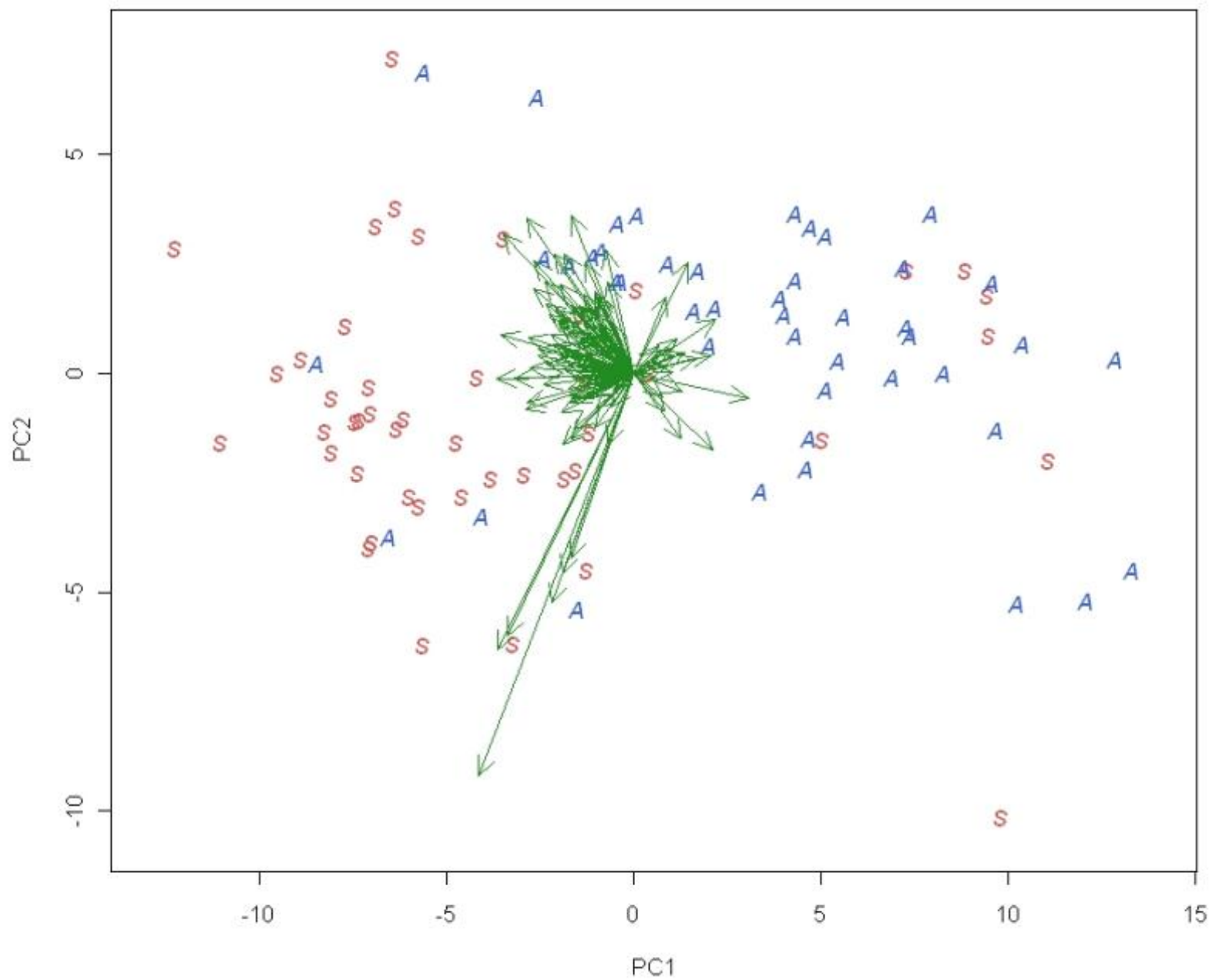


**Adeno = 58, Sqamous = 53**  
**p = 2.54<sup>e-3</sup>**

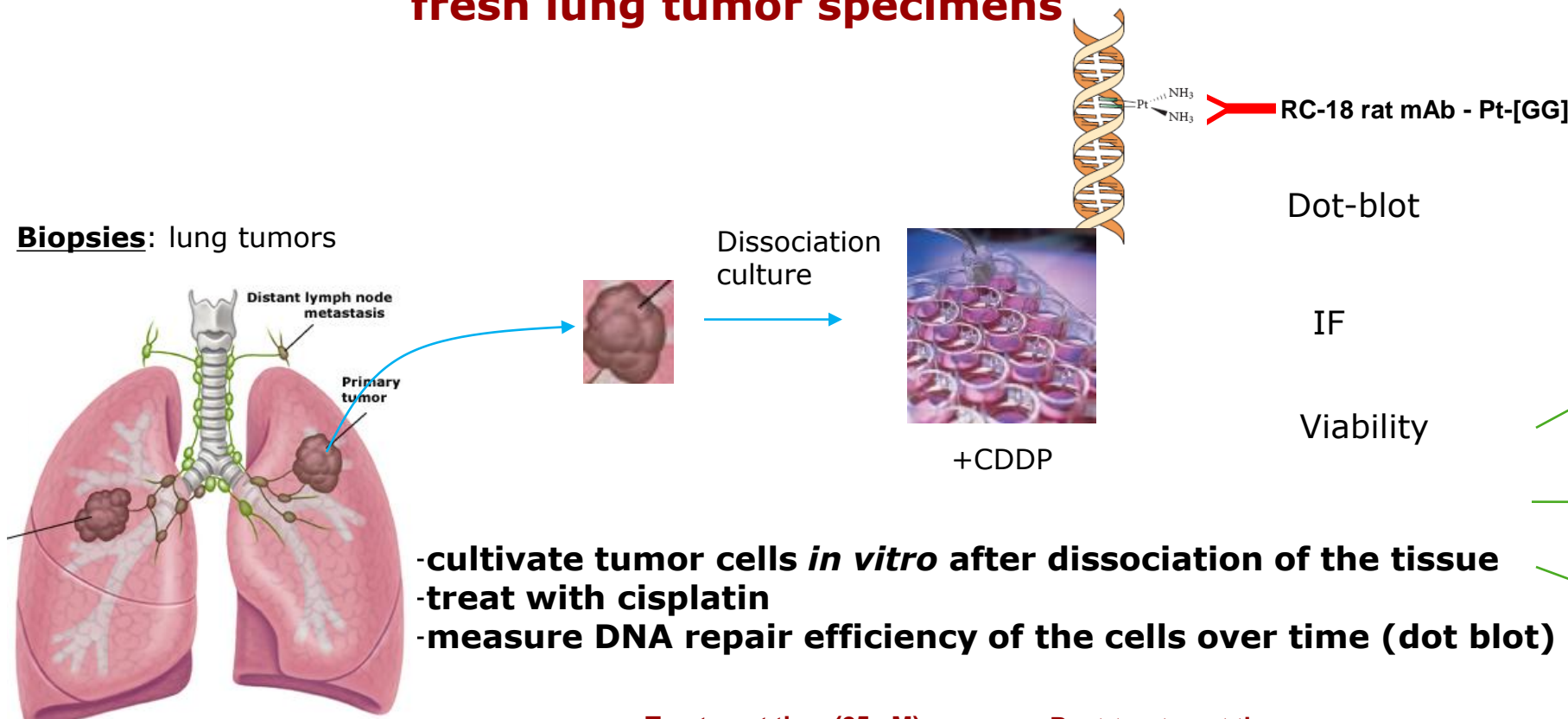
**CHEK1 according to tumor type**  
**Kim data (n=138)**



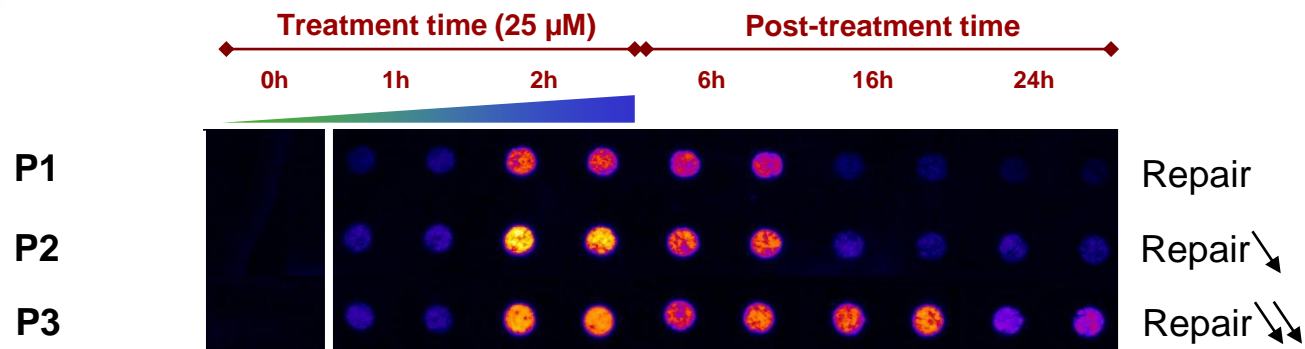
**Adeno = 62, Sqamous = 76**  
**p = 2.17<sup>e-8</sup>**



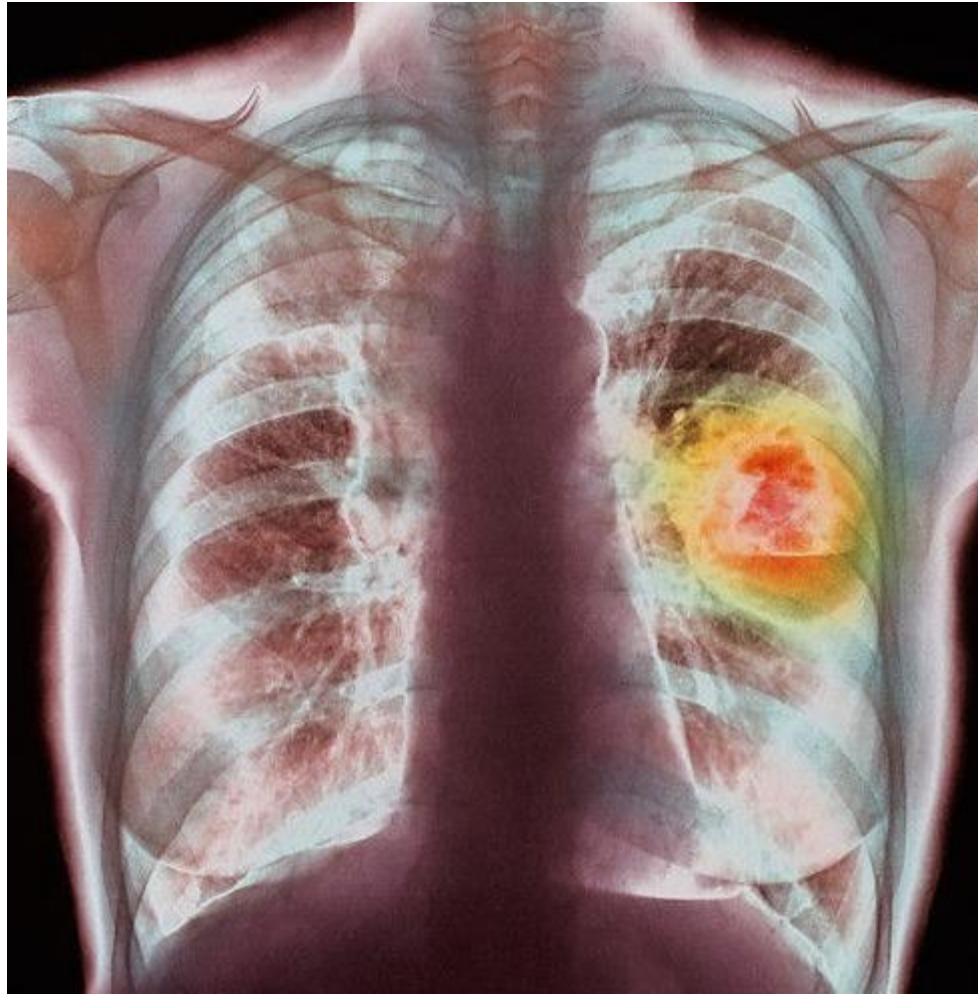
## Application of a functional DNA repair assay on fresh lung tumor specimens

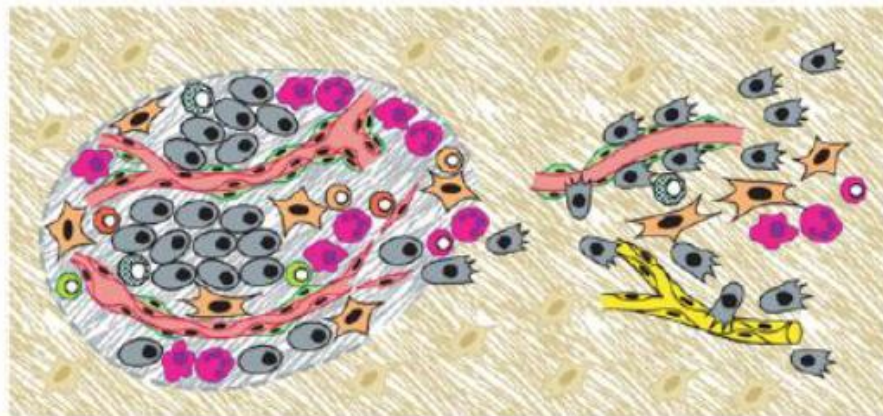
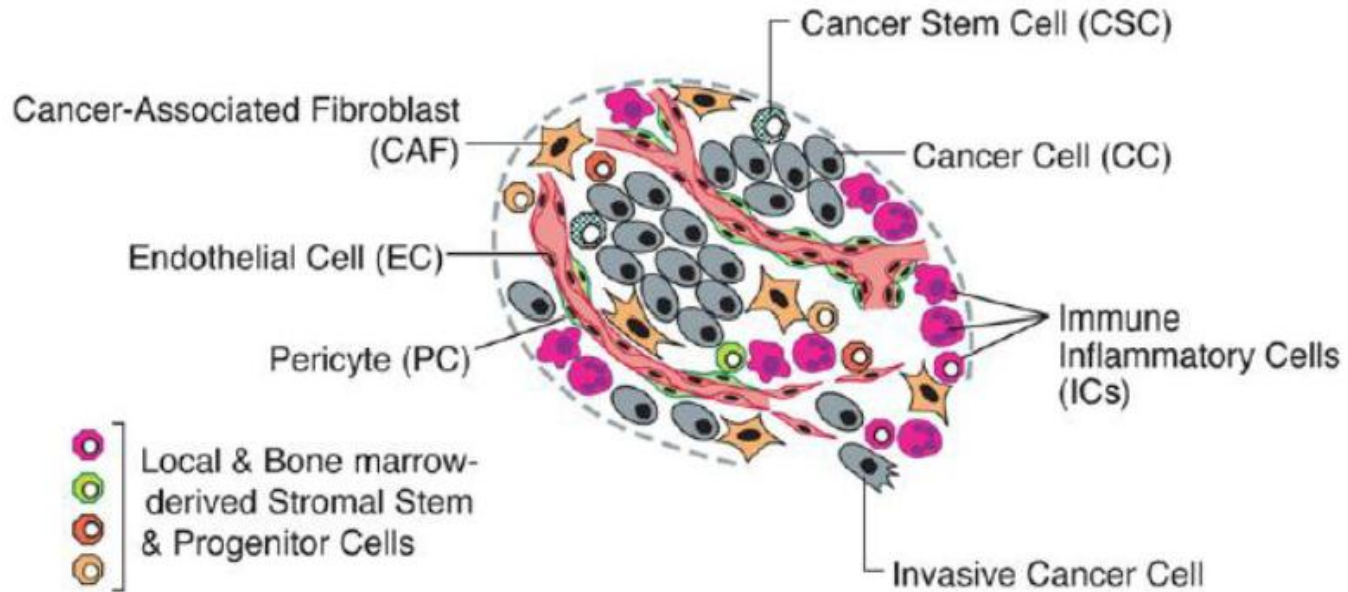


- cultivate tumor cells *in vitro* after dissociation of the tissue
- treat with cisplatin
- measure DNA repair efficiency of the cells over time (dot blot)

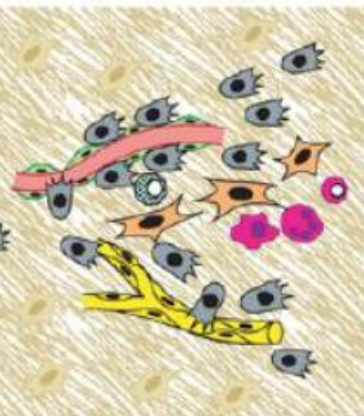




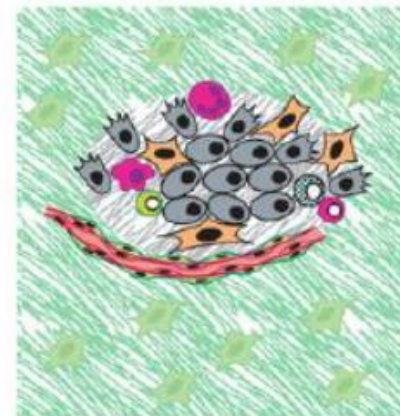




Core of Primary Tumor microenvironment

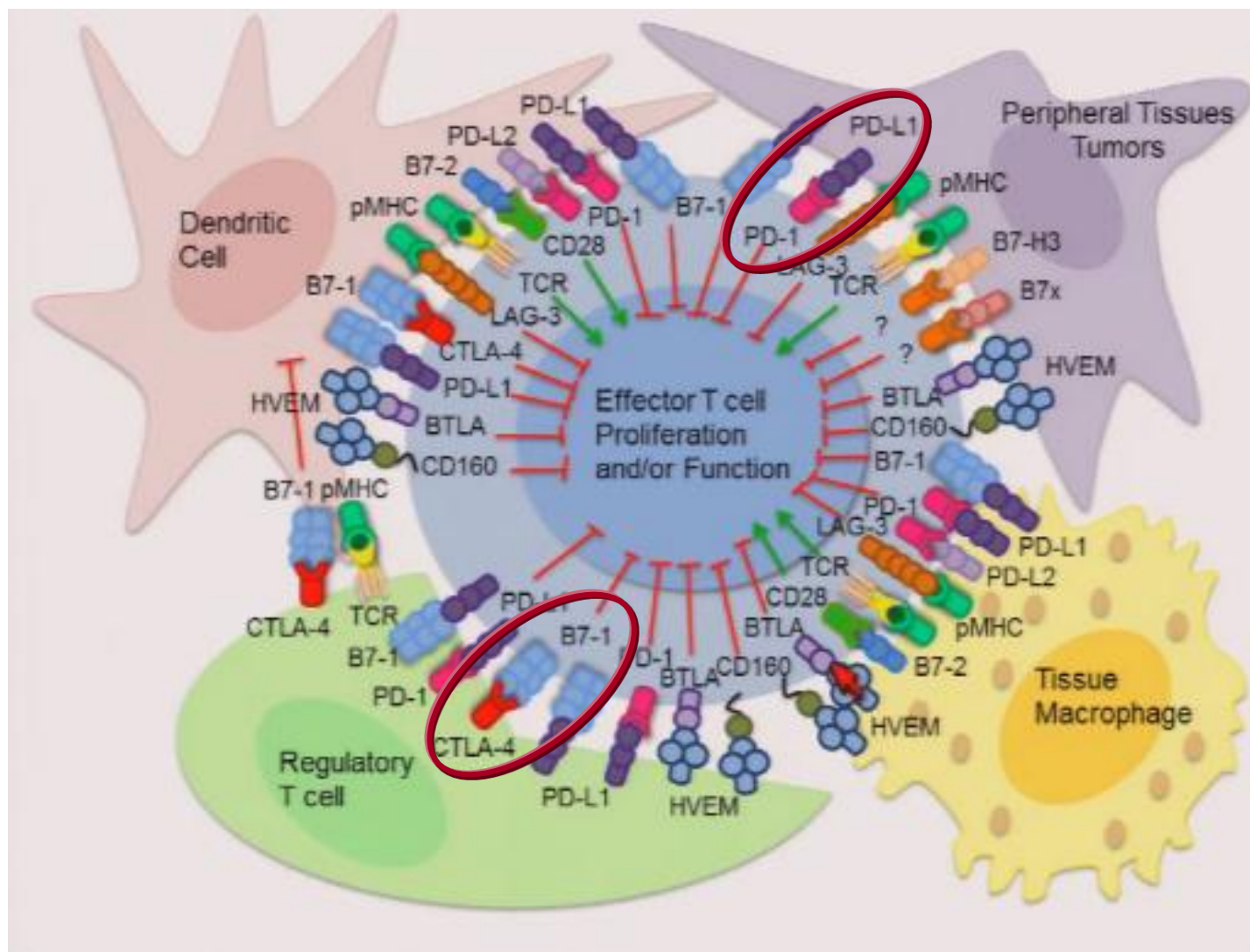


Invasive Tumor microenvironment



Metastatic Tumor microenvironment

Hanahan  
 Weinberg  
 Cell 2011



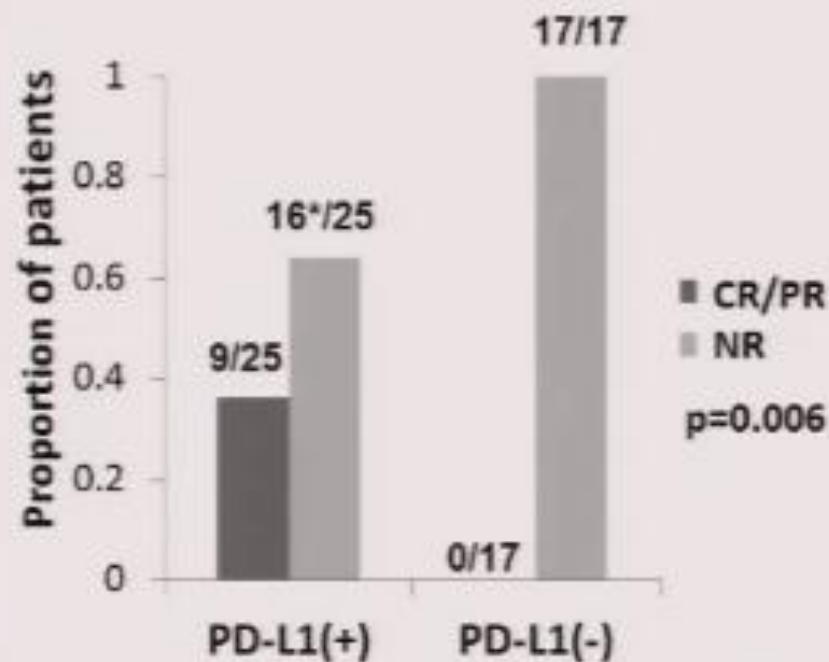
Target	Antibody	Molecule	Company	Development stage
PD-1	BMS-936558/MDX-1106/ONO-4538	Fully human IgG4 mAb	Bristol-Myers Squibb	Phase II multiple tumors
	CT-011	Humanized IgG1 mAb	CureTech	Phase II multiple tumors
	MK-3475	Humanized IgG4 mAb	Merck	Phase I
	AMP-224	B7-DC/IgG1 fusion protein	Amplimmune	Phase I
PD-L1	MDX-1105/BMS-936559	fully human IgG4 mAb	Bristol-Myers Squibb	Phase I
PD-L1	MPDL3280A	fully human IgG1 mAb	Genentech	Phase I



## Clinical Activity of PD1 Antibody

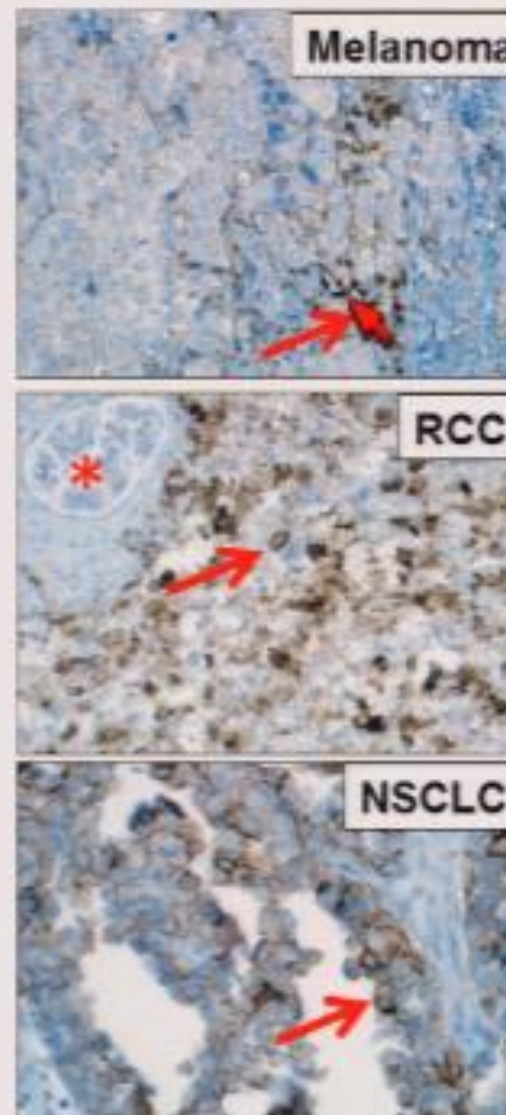
Parameter	BMS-936558 Dose, mg/kg		
	1	3	10
<b>ORR, No. patients* (%)</b>			
Squamous	0 n=5	3 (50) <b>6/18 = 33% (95%CI 13%-59%)</b>	3 (13)
Non-squamous	0 n=1	3 (23) <b>7/56 = 12.5% (95%CI 5%-24%)</b>	4 (13)
<b>SD ≥24 wk, No. patients (%)</b>			
Squamous	0	0	0
Non-squamous	1 (8)	2 (15)	2 (6)
<b>PFSR at 24 wk, (%)</b>			
Squamous	0	50	43
Non-squamous	14	37	21

## Correlation of PD-L1 expression in pretreatment tumor biopsies with clinical outcomes



42 pts include 18 MEL, 10 NSCLC, 7 CRC, 5 RCC, and 2 CRPC.

\*2 pts still under evaluation



# The path of survival of NSCLC patient

## Specific mutation/amplification

## MOLECULAR PORTRAIT

- Sequencing
- CGH, FISH

EGFR	→	Gefitinib/Erlotinib/Afatinib
ALK, ROS	→	Crizotinib
HER2	→	Trastuzumab
FGFR1	→	BJG398, AZD4547, EOS3810

Lung  
Cancer  
patient

No driver

Histology-driven Tx

No portrait



## The path of survival of NSCLC patient

