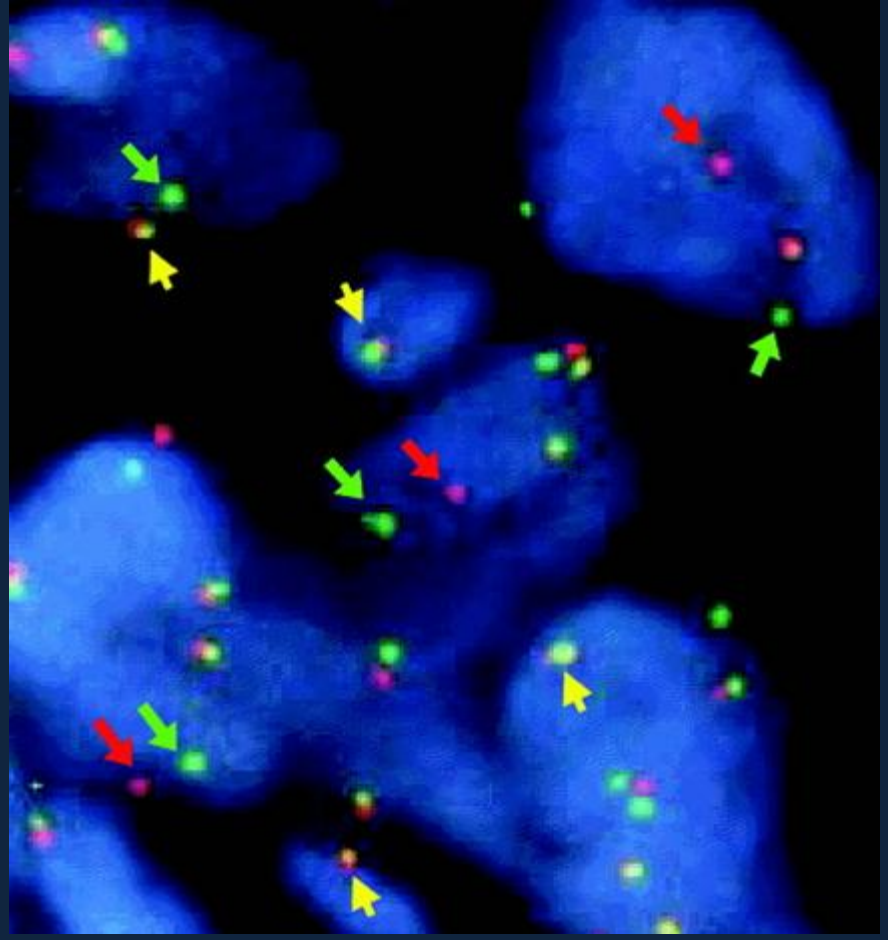
Solange Peters, MD-PhD
Cancer Center, Lausanne
Switzerland

GOING BEYONG EGFR



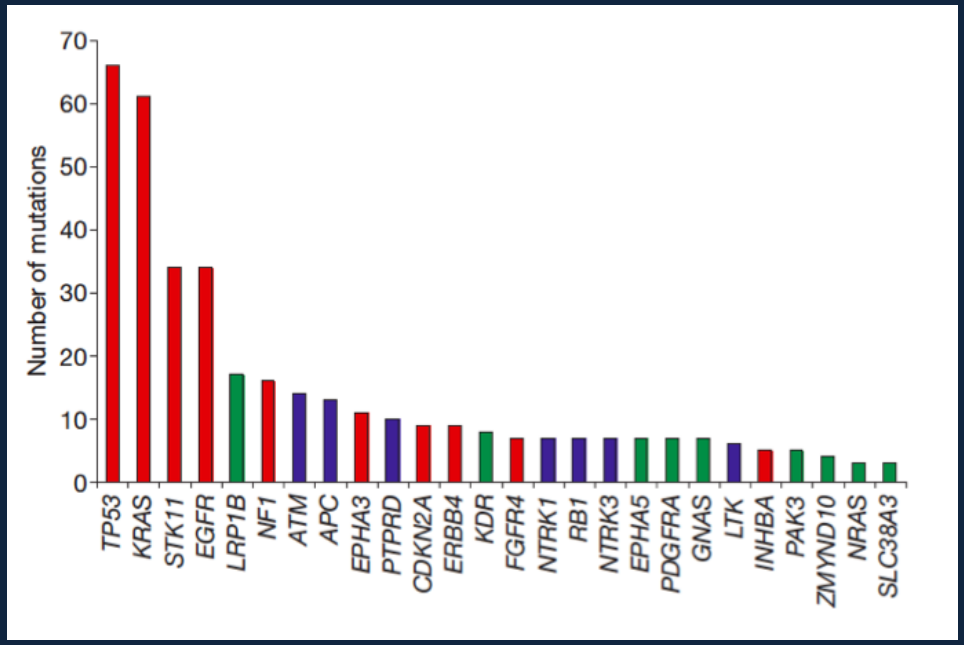
Disclosures

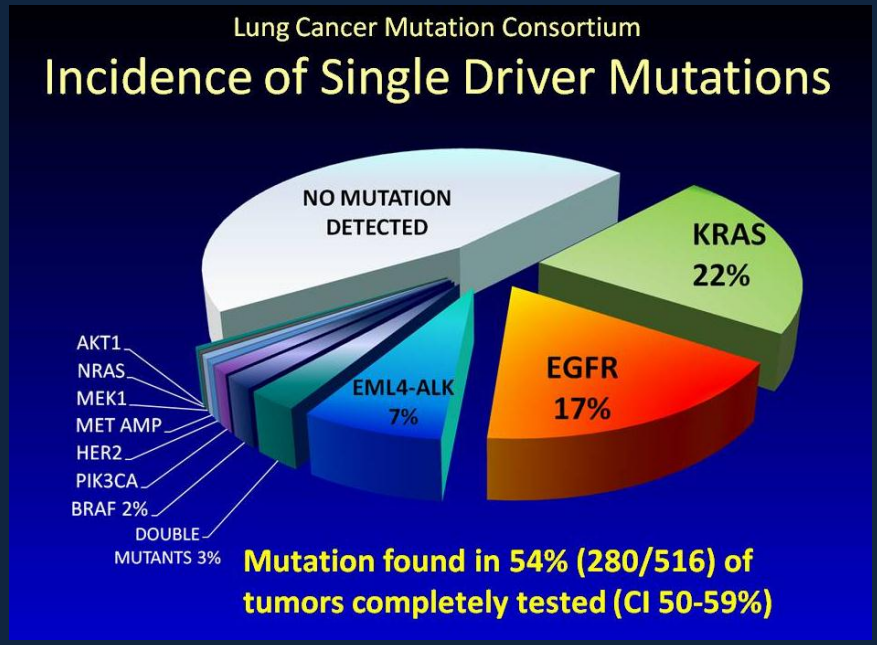
I have provided consultation, attended advisory boards and/or provided lectures for:

F. Hoffmann–La Roche, Ltd; Eli Lilly and Company Oncology, AstraZeneca, Pfizer, Boehringer-Ingelheim, BMS, Daiichi-Sankyo, Morphotek, Merrimack and Merck Serono; for which I received honoraria.

I declare no conflict of interest.

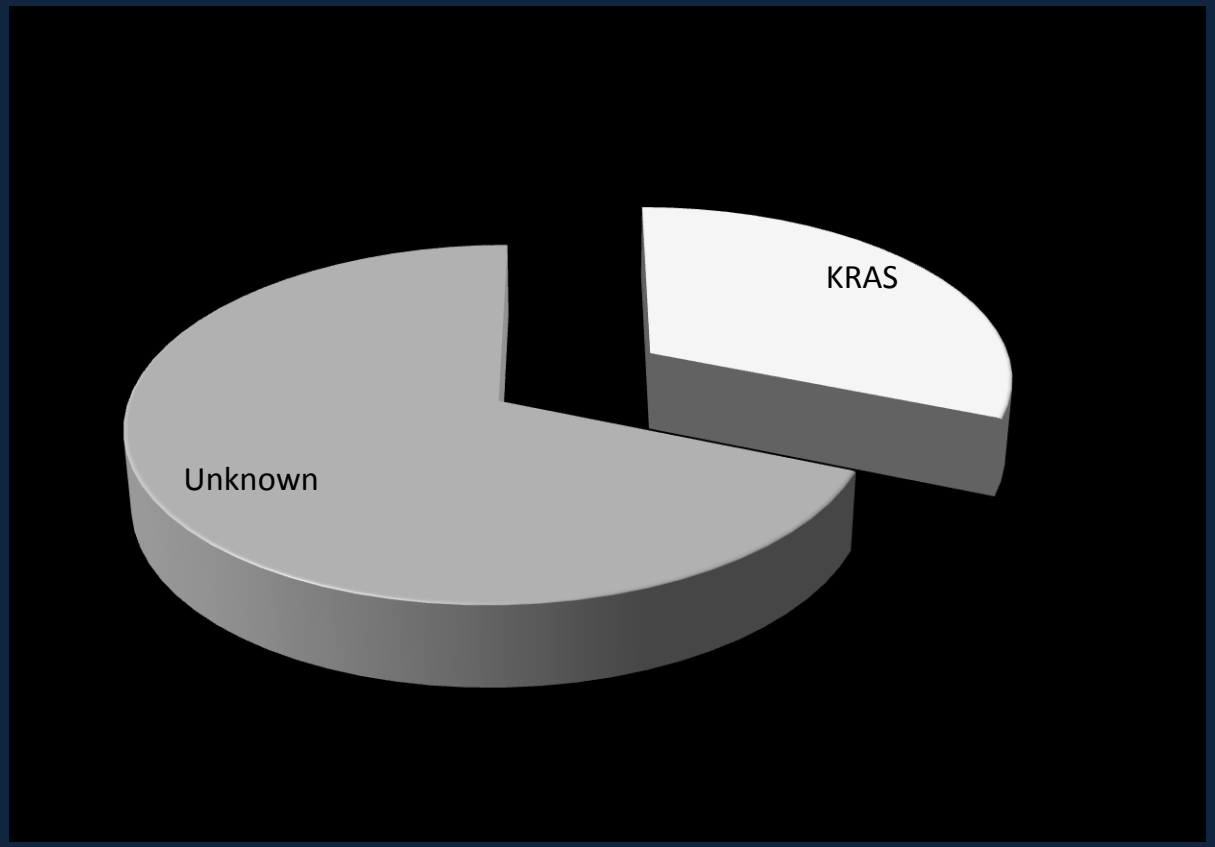
Landmark NSCLC genetic maps



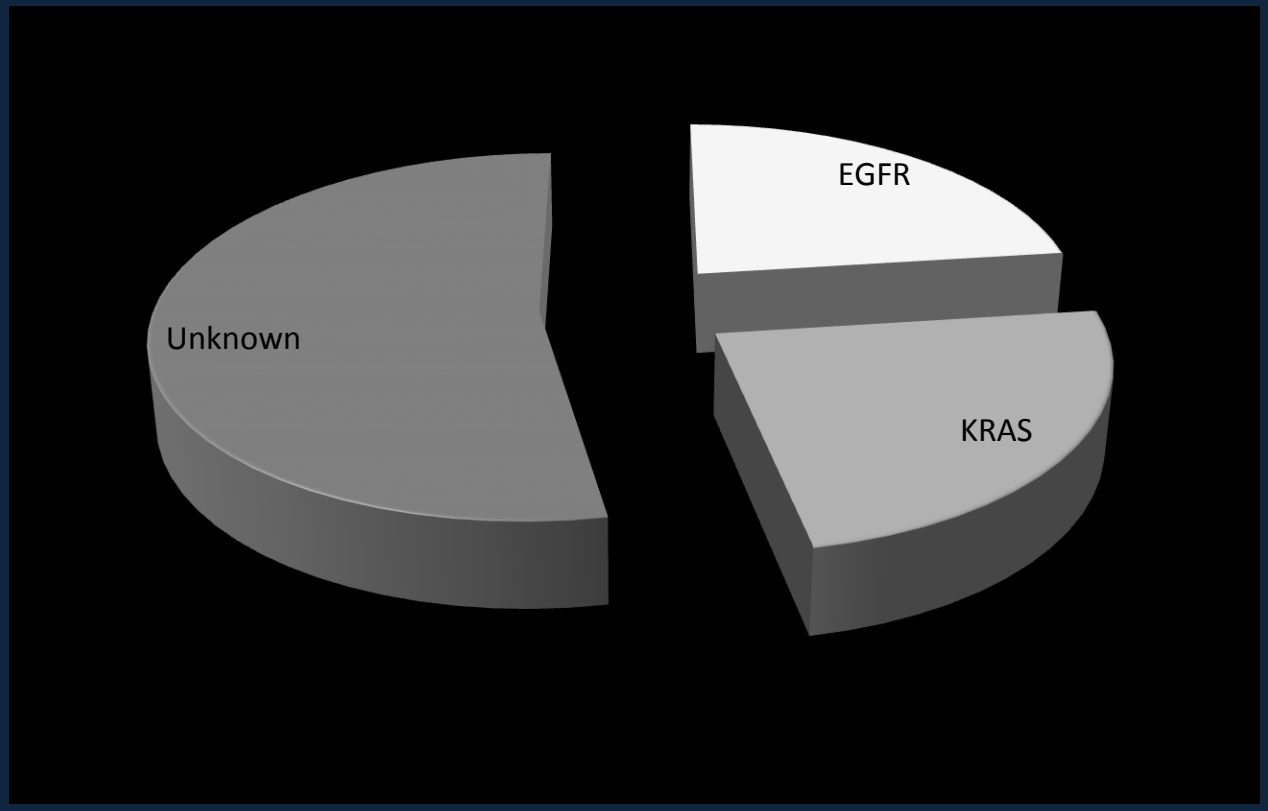


Ding, Nature 2008; Kris, ASCO 2011

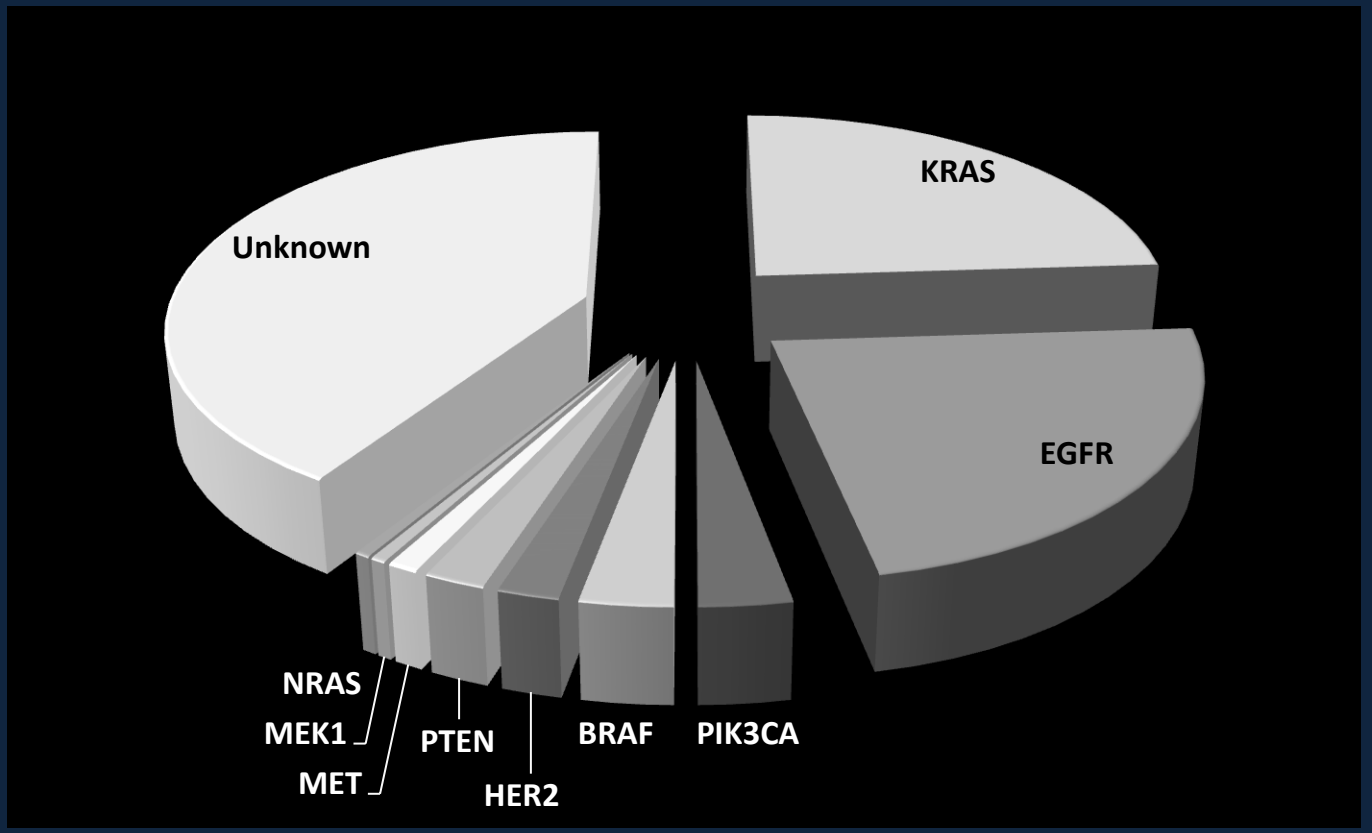
Adenocarcinoma driver mutations: 1990



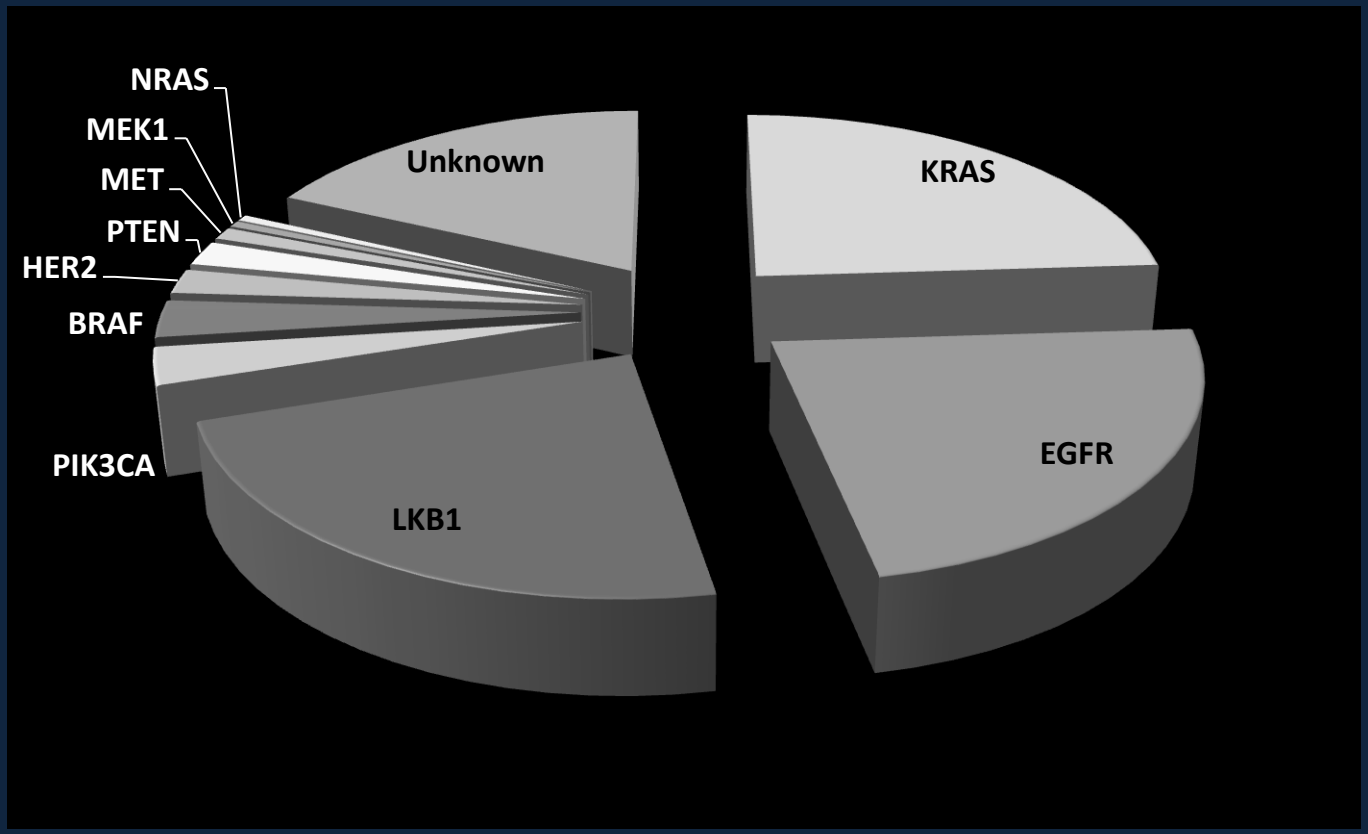
Adenocarcinoma driver mutations 2004-2008



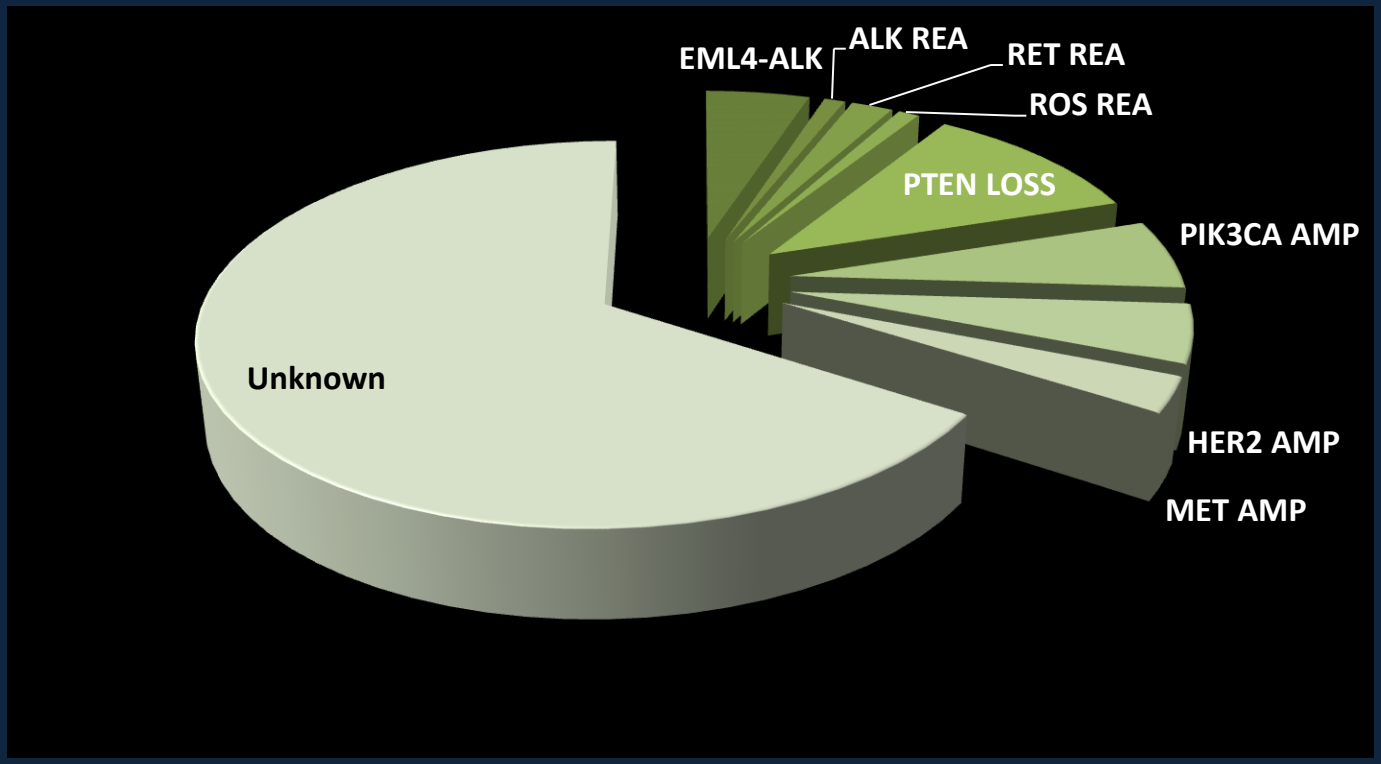
2012 update on adenocarcinoma driver mutations



2012 update on adenocarcinoma driver mutations
Where to add tumour suppressors?

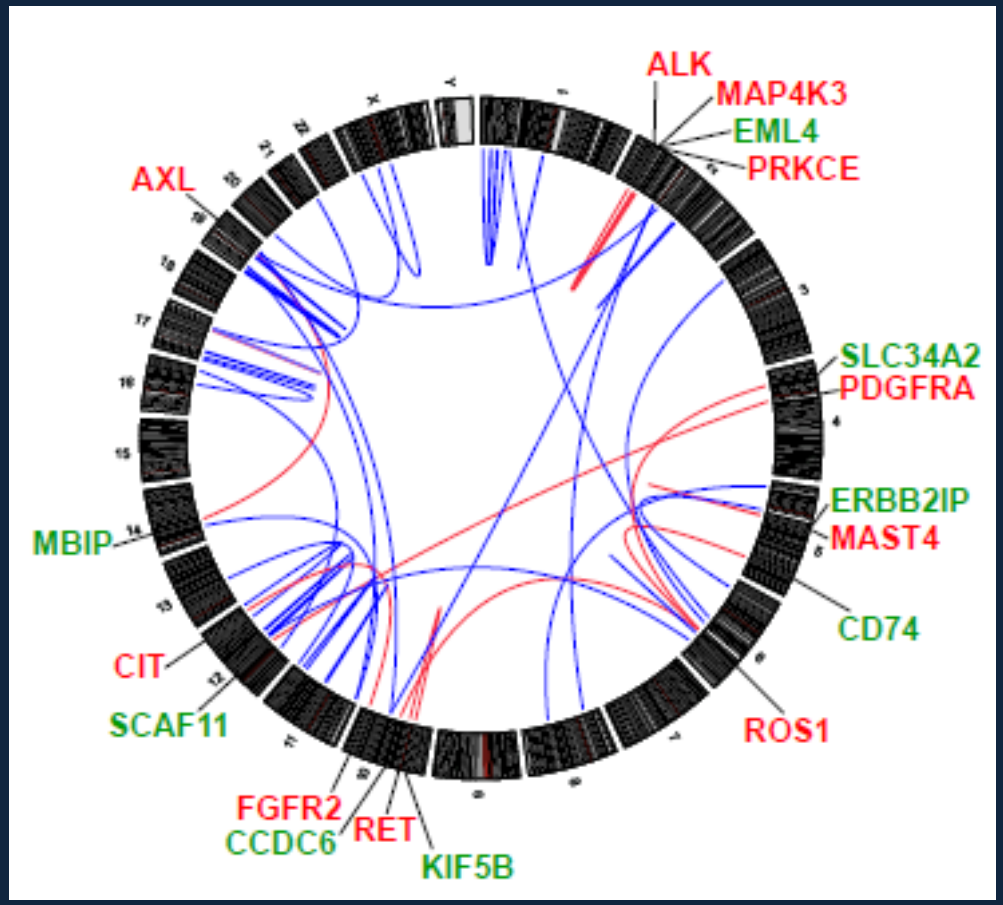


2012 update on adenocarcinoma driver quantitative alterations



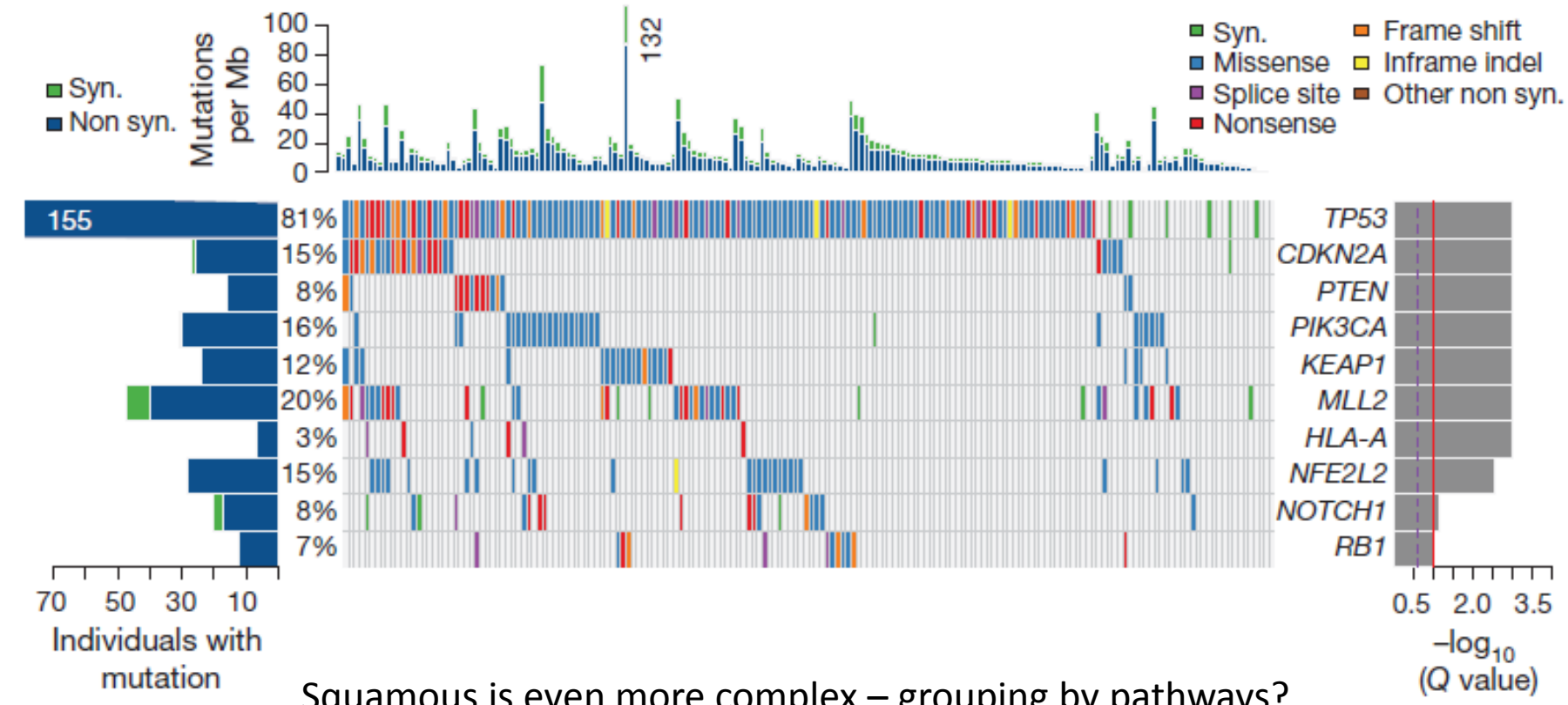
2012 update on driver rearrangements
The complex picture

Graphical representation of 45 fusion genes from 87 adenocarcinomas



Seo, Genome Res 2012

2012 update on squamous carcinoma driver mutations/ quantitative alterations

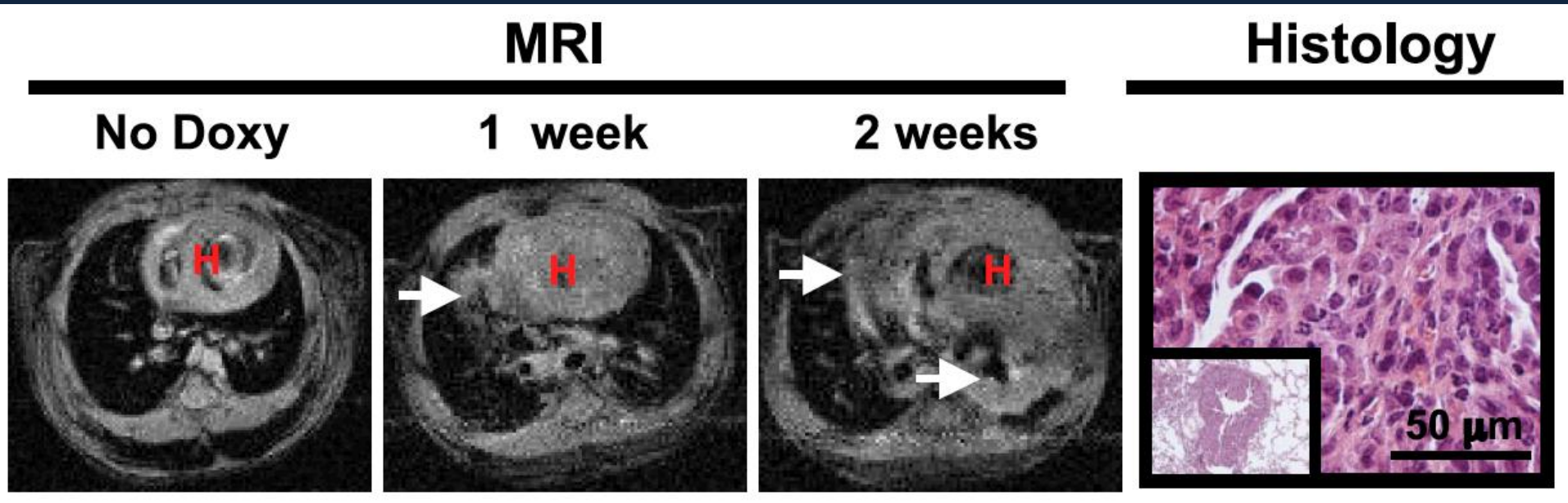


Squamous is even more complex – grouping by pathways?

Prez-Moreno, CCR 2012; Paik, ASCO 2012, TCGA, Nature 2012

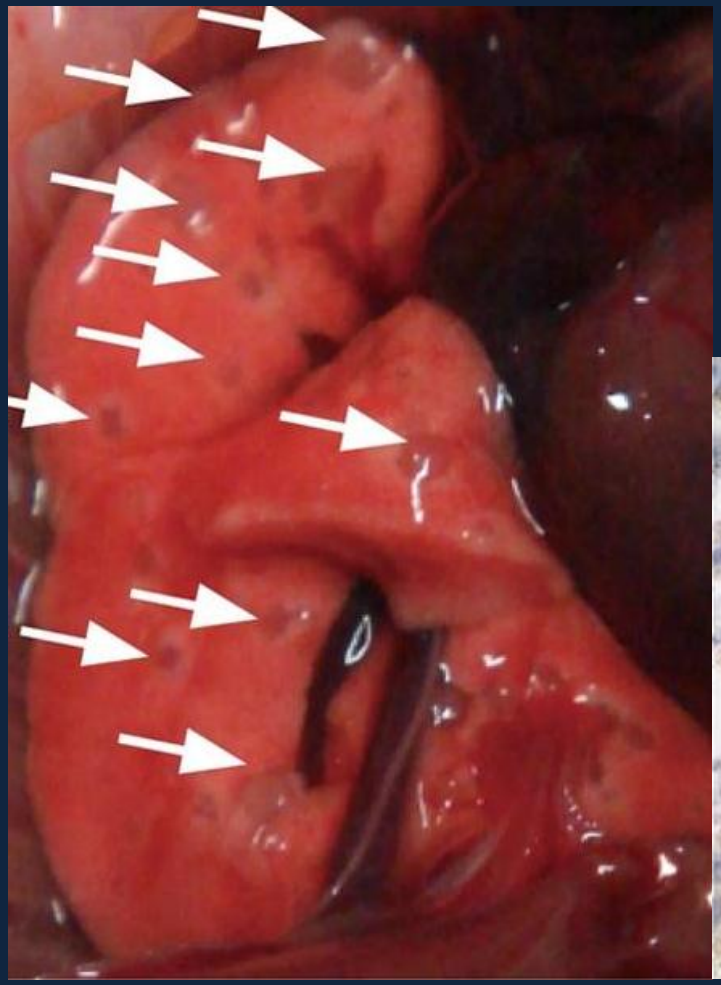
Definition of drivers?

HER2 mutation (HER2YVMA):
Drives rapid development of adenosquamous lung tumors in mice

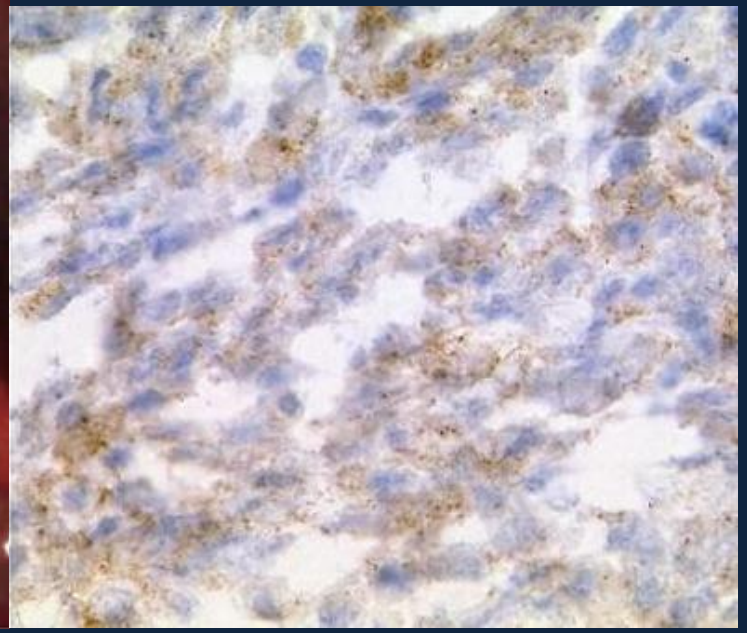


Perera, PNAS 2009

Definition of drivers (2)?



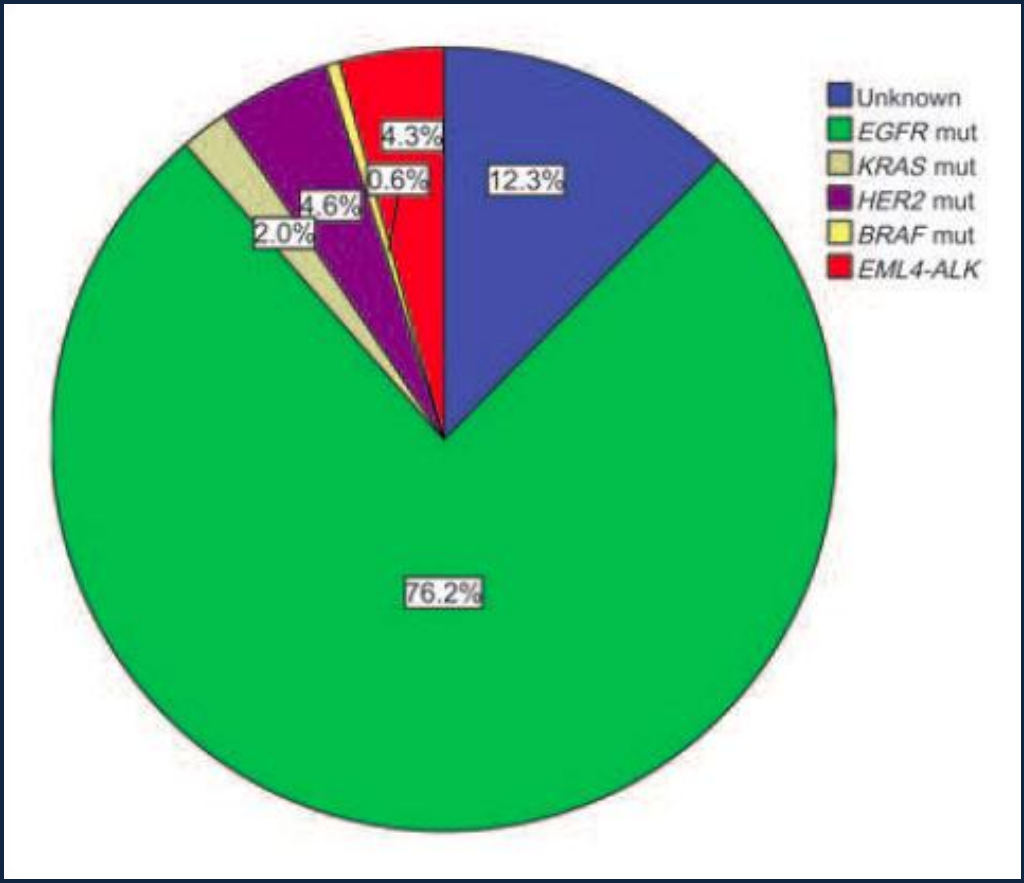
Development of lung adenocarcinoma in ***EML4-ALK*** transgenic mice:
Hundreds of adenocarcinoma nodules (arrows)



Soda, PNAS 2008

Drivers prevalence variability?

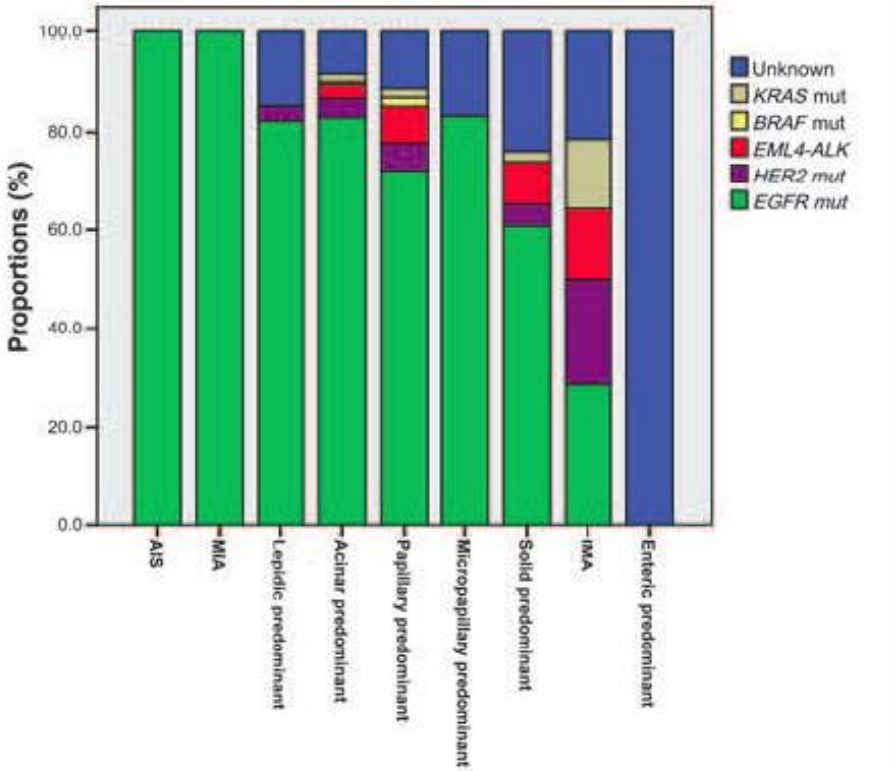
Frequency of Driver Mutations in Lung Adenocarcinoma from Female Never-Smokers …

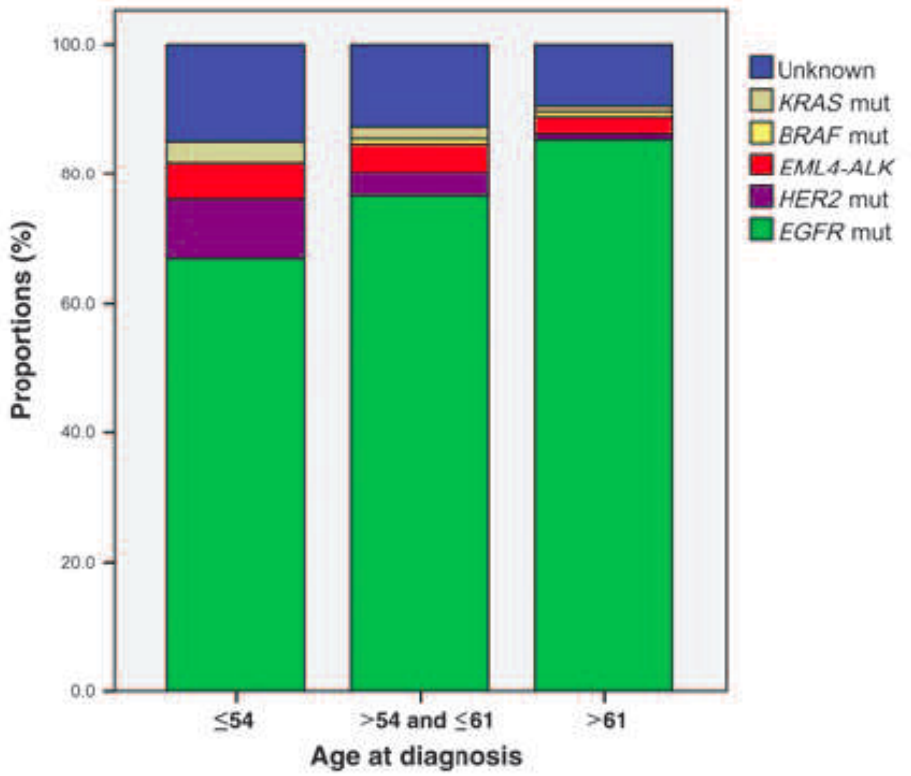


Zhang, CCR 2011

Drivers prevalence variability (2)?

Frequency of Driver Mutations in Lung Adenocarcinoma from Female Never-Smokers … **varies with age, and histologic subtype**





Zhang, CCR 2011

Conclusion 1

Most patients with lung cancer will be stratified according to one (or more) oncogenic driver in the future. Potential therapeutic targets are also identified in squamous carcinoma – with a marked genomic complexity.

NEVERTHELESS:

- Driver alteration prevalence varies according to several demographic parameters – which remains to be explained

- Cancers harbouring identical alterations show large variations in response to the same targeted therapy demonstrating hidden and additional complexity

Mutual exclusivity (1)

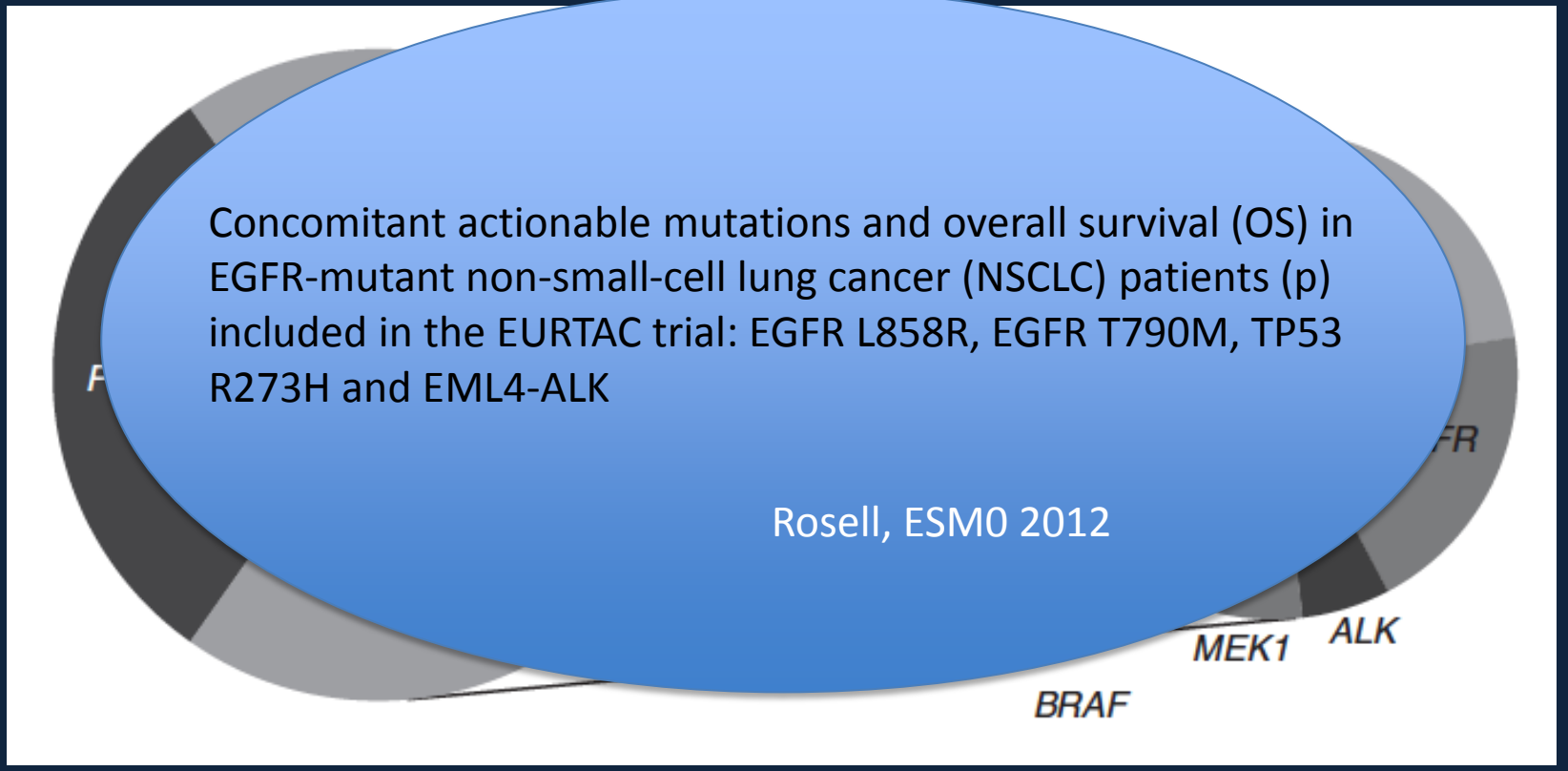
Key findings: 97% of mutations mutually exclusive

# Single mutations	ALK	AKT	BRAF	EGFR	HER2	KRAS	MEK1	MET	NRAS	PIK3CA
ALK (38)	X		1	2		1		1		
AKT1 (0)		X								
BRAF (9)			X							1
EGFR (89)				X				1		3
HER2 (3)					X					
KRAS (114)						X		1		
MEK1 (2)							X	1		1
MET AMP (3)								X		
NRAS (2)									X	
PIK3CA (6)										X

Number of patients with variants in indicated combination of genes, 3% (14/516)

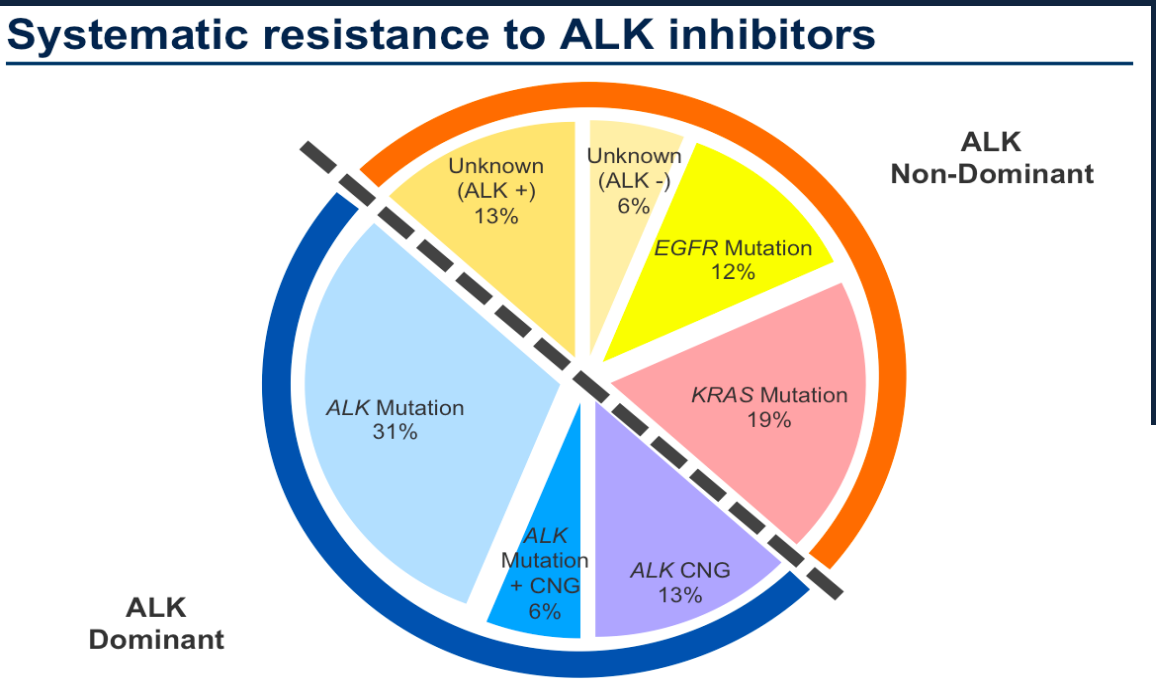
Kris, ASCO 2011

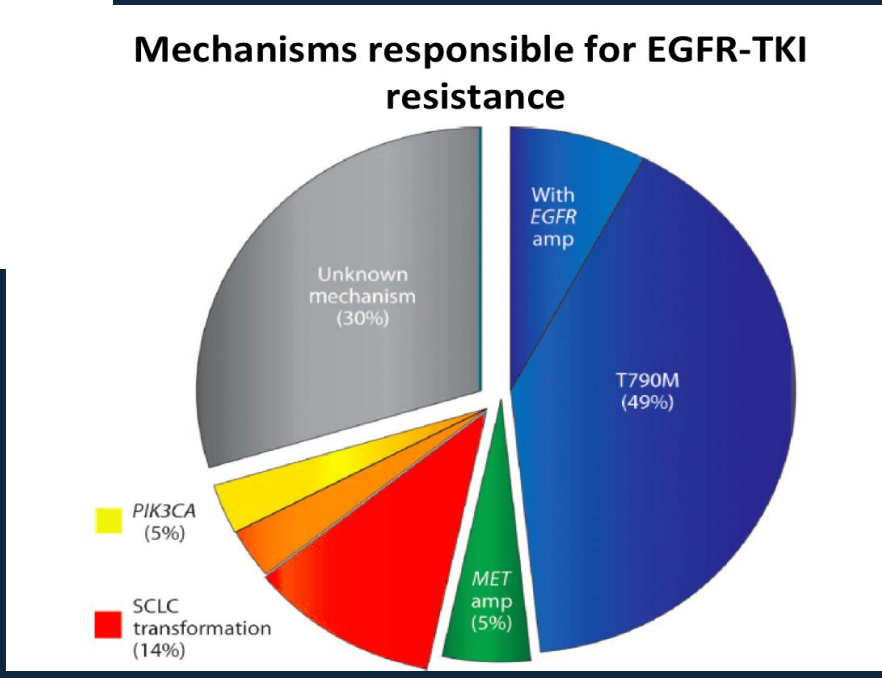
Mutual exclusivity (2)



Chaft, Mol Cancer Ther 2011

Co-existence proof: at resistance





Doebele, ASCO 2012; Sequist et al, Science Transl Med 2011

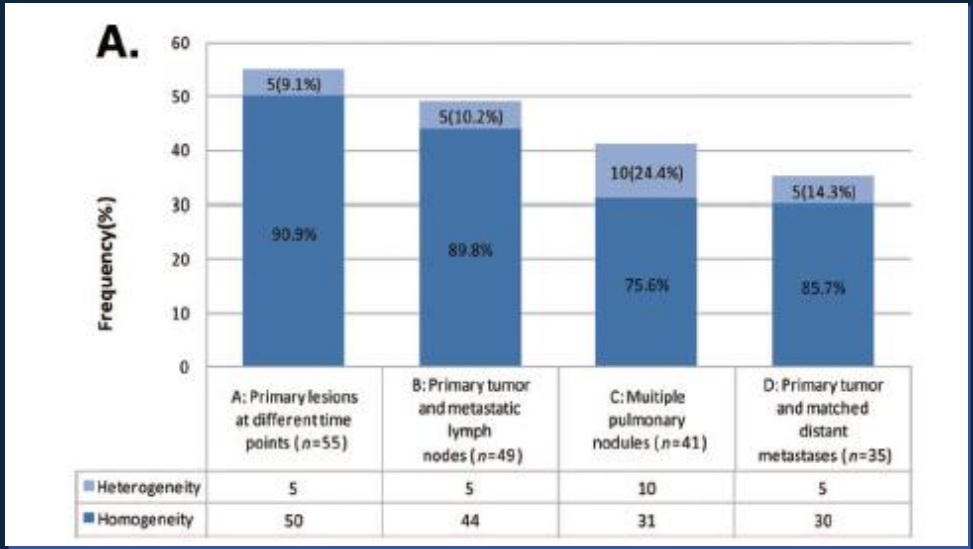
Conclusion 2

Distinct oncogenic drivers are found concomitantly in the same tumour, as proven for ALK, EGFR, MET, PIK3CA as well as for alterations of tumour suppressor genes.

HOWEVER:

- Molecular diagnosis remains strongly dependant of detection method sensitivity (clinical significance threshold?)
- Impact of co-existing genetic mutations, especially regarding tumour suppressor genes, remains to be explored
- No evidence to guide treatment choice in the context of multiple coexisting drivers is available

Heterogeneity of driver mutations



Spatial heterogeneity of lesions

Temporal heterogenous of tumour cells under selective pressure

Table 2. Effect of First-Line Chemotherapy on *EGFR* Mutation Status Before and After Treatment in Plasma Samples From Patients With Stages IIIb to IV NSCLC (n = 264)

	Postchemotherapy					
	Wild Type		Mutated		Total	
Prechemotherapy	No.	%	No.	%	No.	%
Wild type	149	56.4	24	9.1	173	65.5
Mutated	54	20.5	37	14.0	91	34.5
Total	203	76.9	61	23.1	264	100.0

NOTE. $P < .001$ (McNemar test).
Abbreviation: NSCLC, non–small-cell lung cancer.

Chen, Oncologist 2012; Bai, JCO 2012

Conclusion 3

Distinct oncogenic drivers can therefore be multiple and heterogenous, vary over time, under drug pressure and upon resistance to targeted agents

NEVERTHELESS:

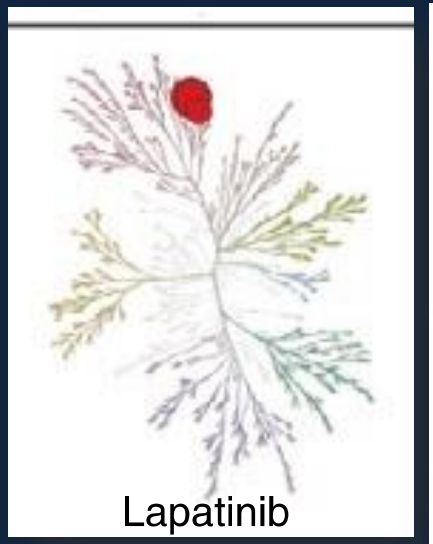
- In selected populations, we have very good efficiency data regarding customised treatment to a single driver
- If we all believe combination targeted treatment will be promising, timing and schedules will be the next issues to solve

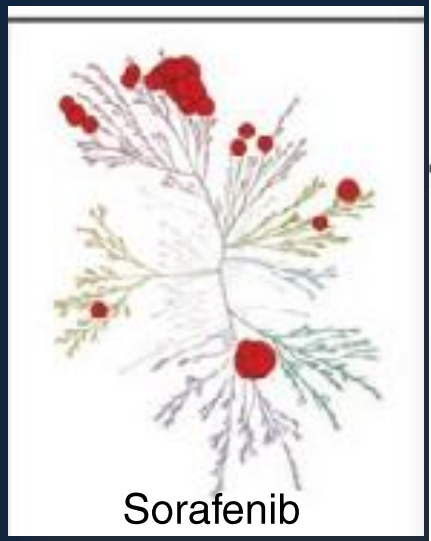
Translation in the clinic

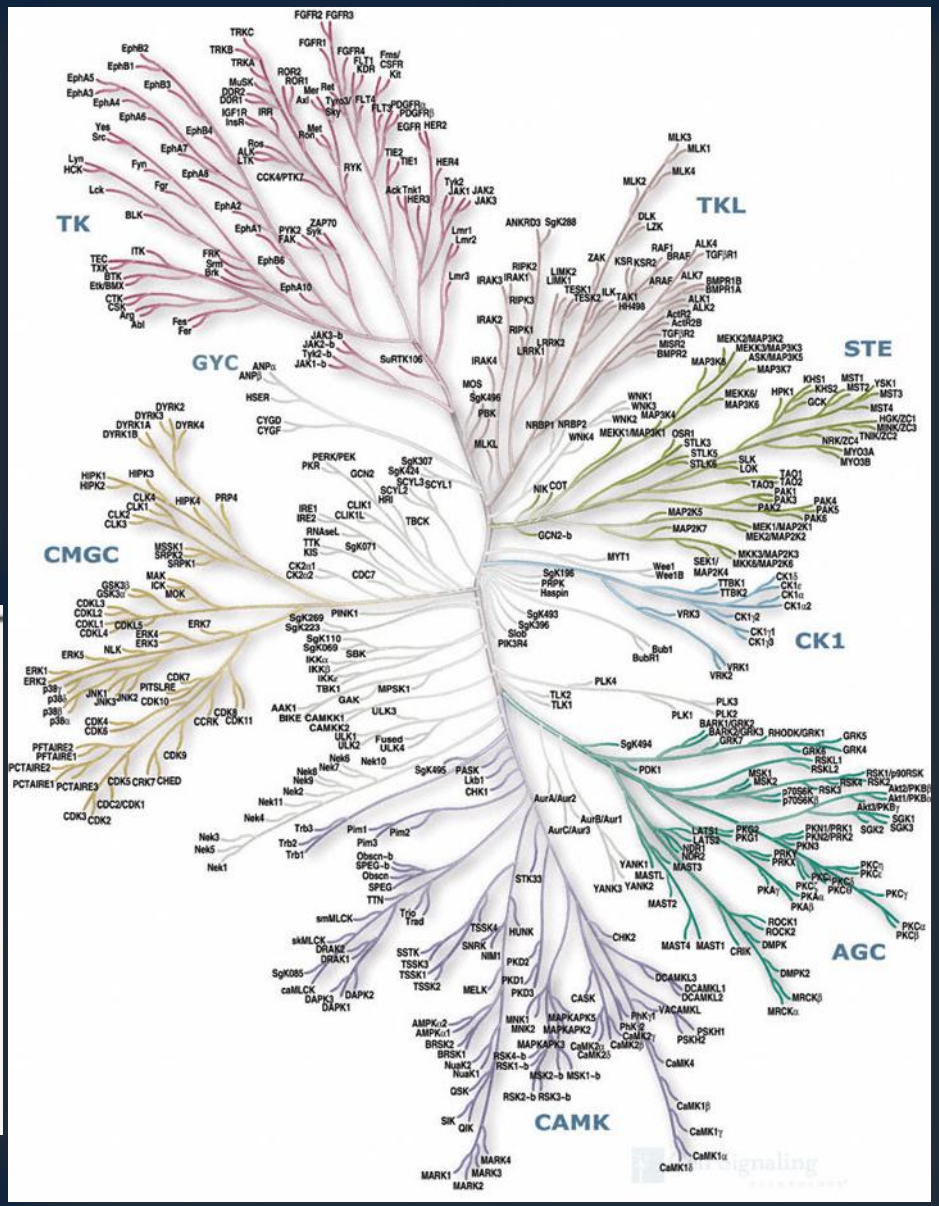
TREATMENT TARGETS AS EXAMPLES

- ALK
- ROS
- RET
- BRAF
- HER2
- FGFR1
- KRAS

Making the best use of off–target activites of TKIs

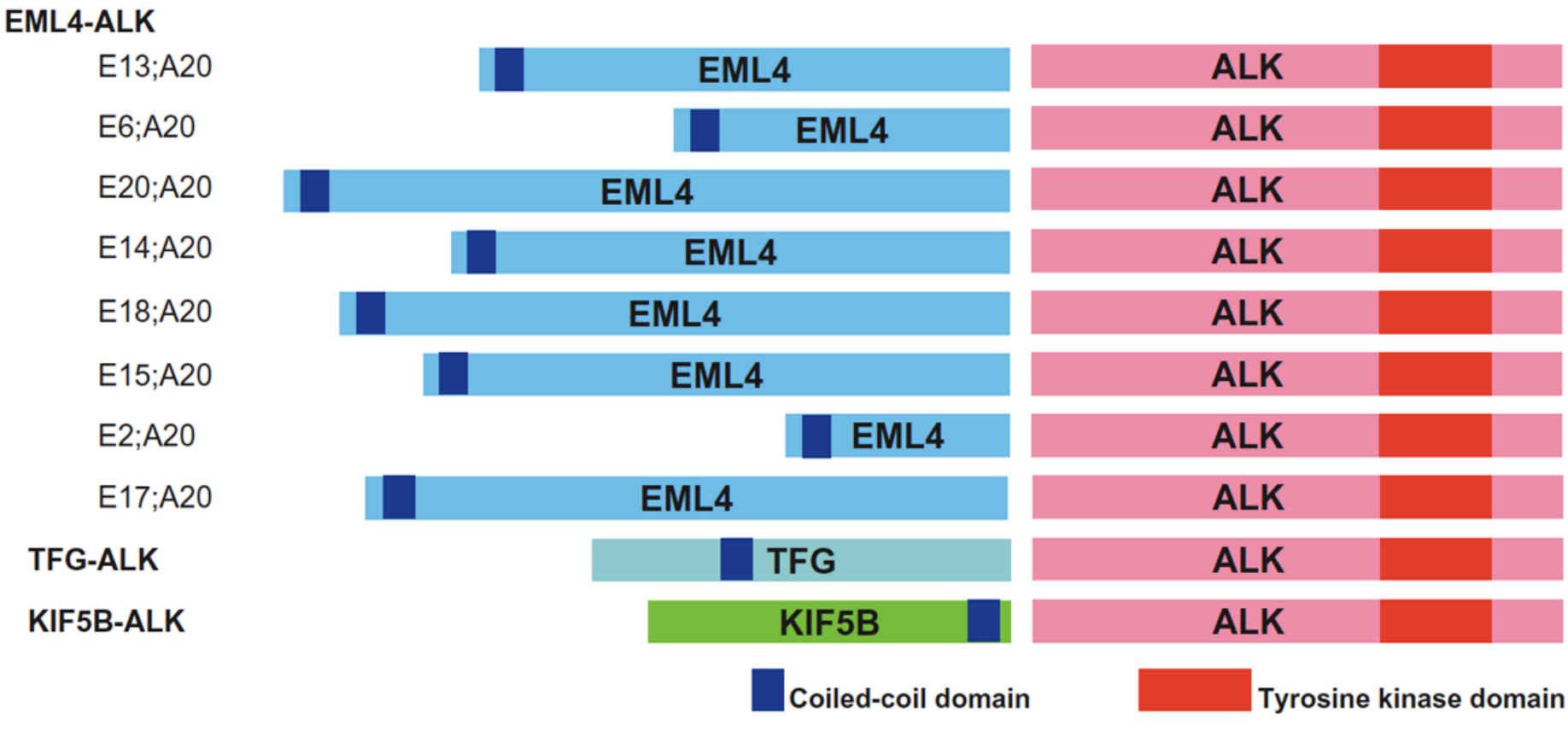






Karaman, *Nature Biotech.* 2008

Translation in the clinic: targeting ALK



Targeting ALK (2)

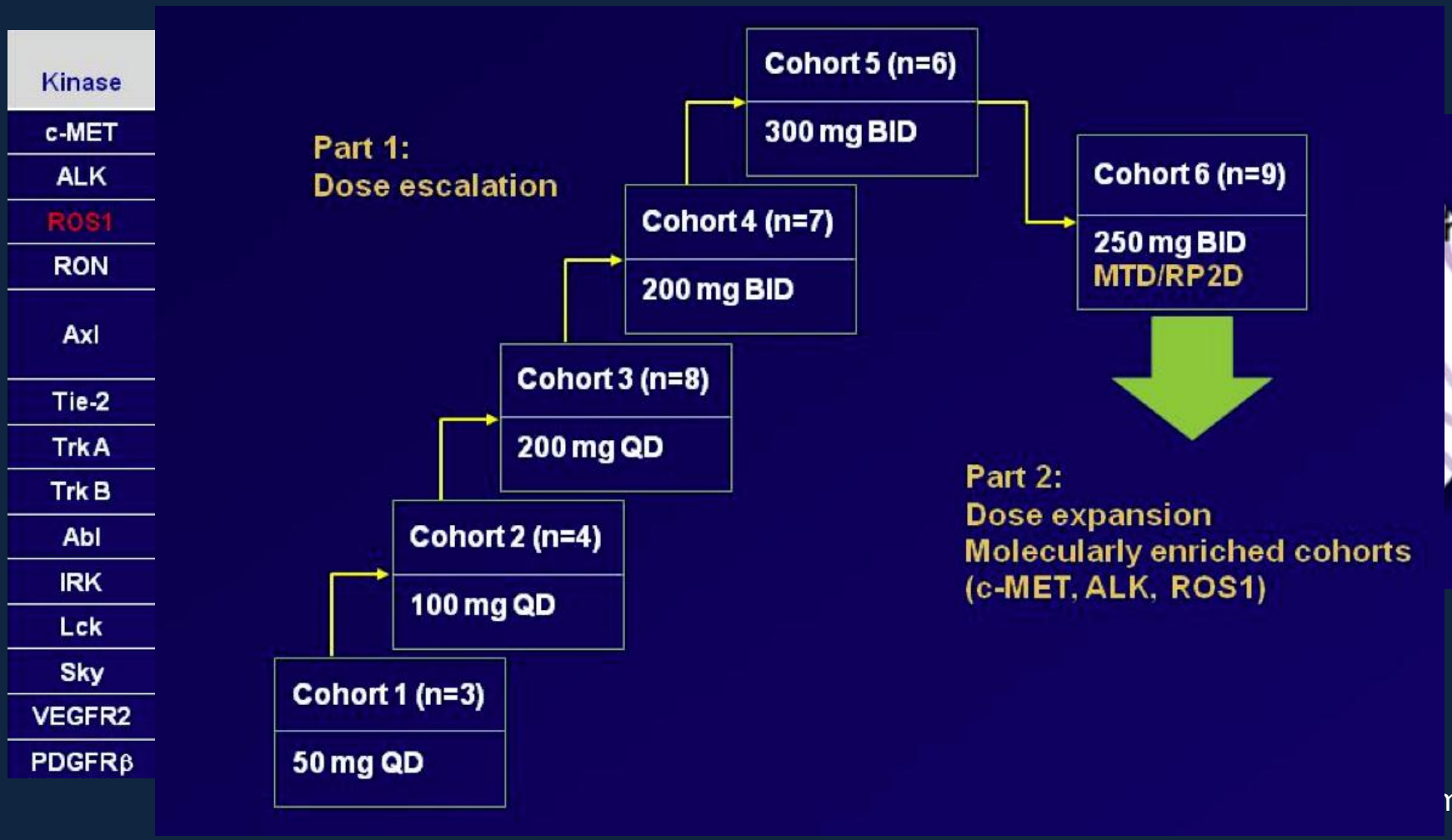
Prevalence in NSCLC: Retrospective Data

Higher prevalence in adenocarcinoma, never/light smokers and younger patients

Wong, Cancer 2009.;Perner, Neoplais 2008; Boland, JTO 2011; Paik, JTO 2011; Takeushi Nat Med 2011; Takahashi Ann Surg Oncol 2010; Rodig, CCR 2009, Varella Garzia IASLC 2011, Shaw JCO 2009

Targeting ALK (3)

Crizotinib



n 2011

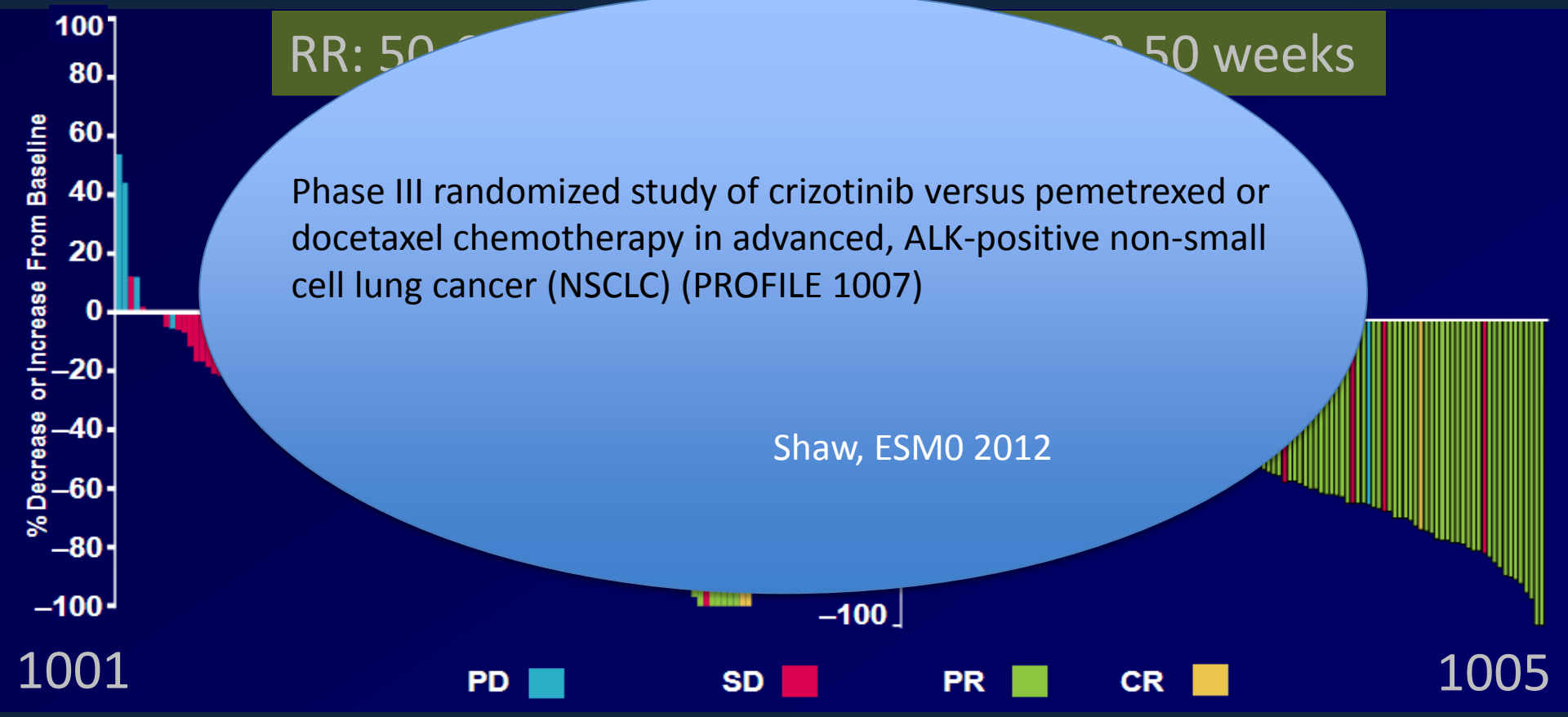
Targeting ALK (3)

Clinical trials program

TRIAL	Population	Phase
PROFILE 1001	ALL -> ALK/MET -> specific cohorts (cave ALK and ROS rearranged NSCLC)	Part 1: dose escalation Part 2: molecular cohorts (NSCLC ALK+ from 2008)
PROFILE 1007	NSCLC ALK +; > 1line	III vs docetaxel or pemetrexed (endpoint PFS)
PROFILE 1005	Not eligible for 1007 or crossover in 1007	II (enpoint ORR)
PROFILE 1014	Not pretreated NSCLC ALK+	III vs pem-platin (endpoint PFS)

Targeting ALK (4)

Activity of crizotinib

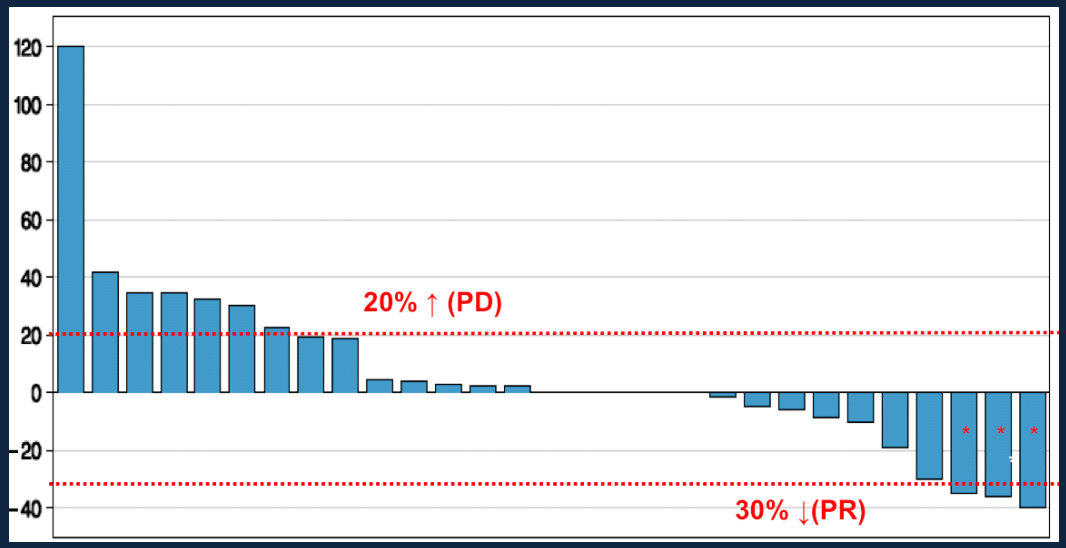


Camidge, ASCO 2011; Riely, IASLC 2011

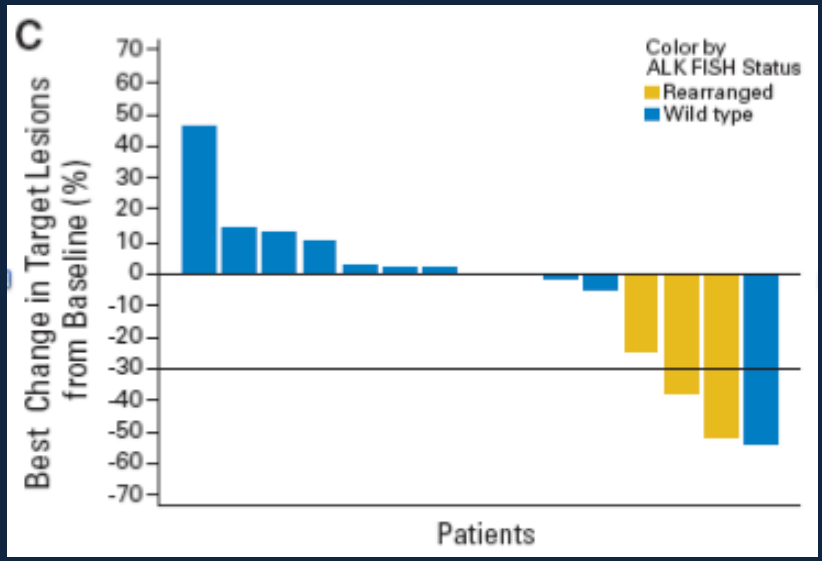
Targeting ALK (5)

Activity of HSP 90 Inhibitors

Mutated EGFR, EML4-ALK, MET, HER2, p-AKT, c-RAF are client proteins of HSP90



Responses in 4/8 patients with ALK (+), crizotinib-naive tumors

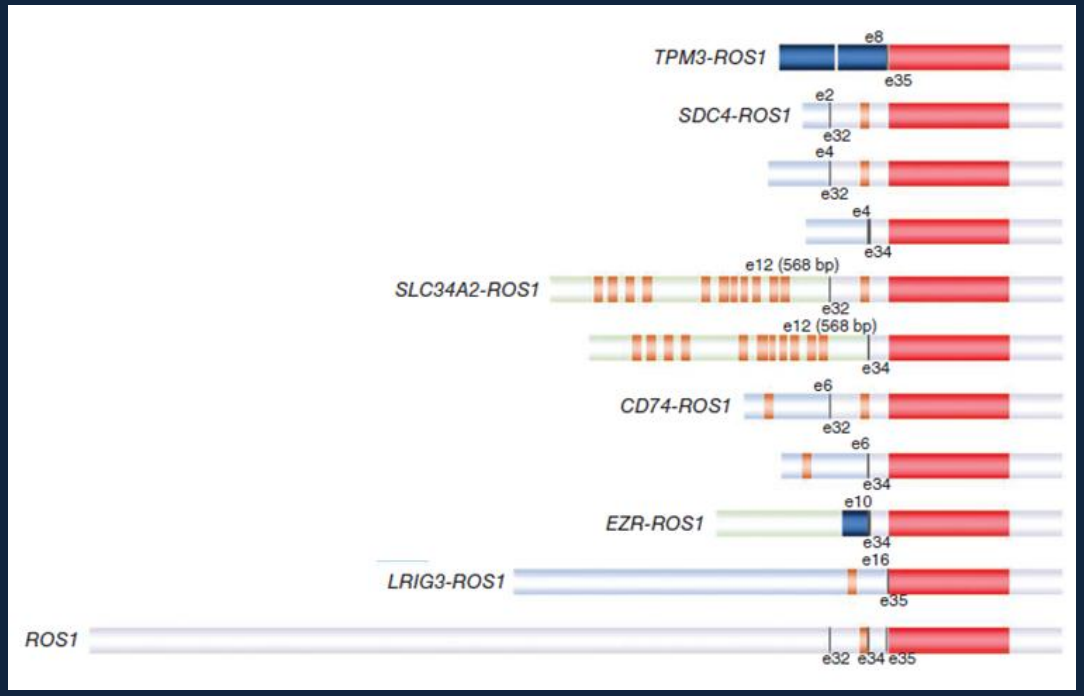


Katayama, Sci Transl Med 2012; Wong , ASCO 2011, Sequist JCO 2010

Translation in the clinic: targeting ROS

ROS1: Receptor tyrosine kinase of the insulin receptor family, little known about its specific function

ROS1 fusion with the transmembrane solute carrier protein SLC34A2 results in a constitutive kinase activity in a NSCLC cell line



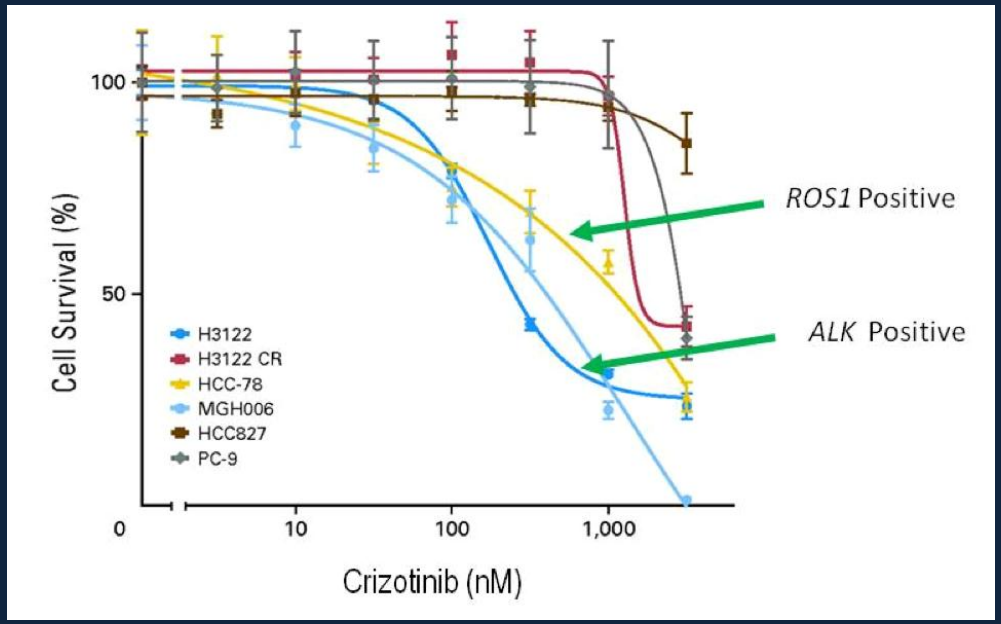
Rikova, Cell 2007; Takeuchi, Nat Med 2011; Bergethon JCO 2012

Targeting ROS (2)

ROS1 fusions in 0.9% (13 out of 1,476) of NSCLC and 1.2% (13 out of 1,116) of adenocarcinoma

ROS1 fusions in 1.7% (all adenocarcinoma) of 1,073 NSCLC

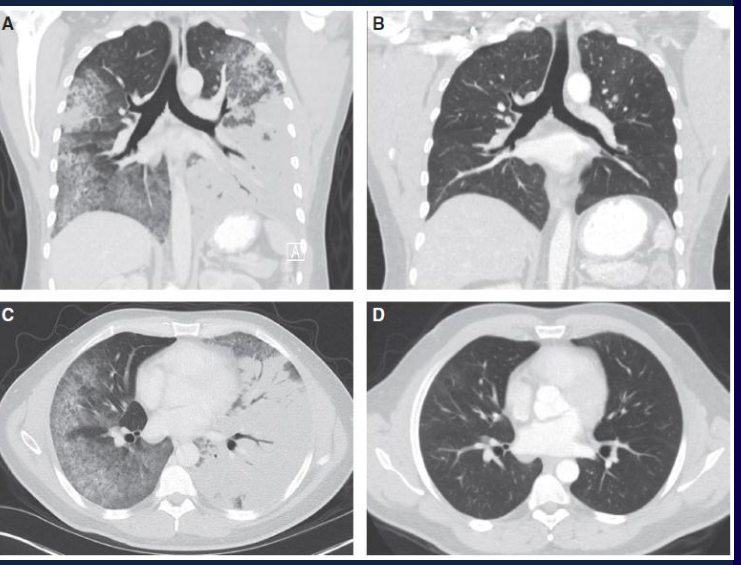
Over-represented: female, adenocarcinma, young (50), never smokers (stage IV?)

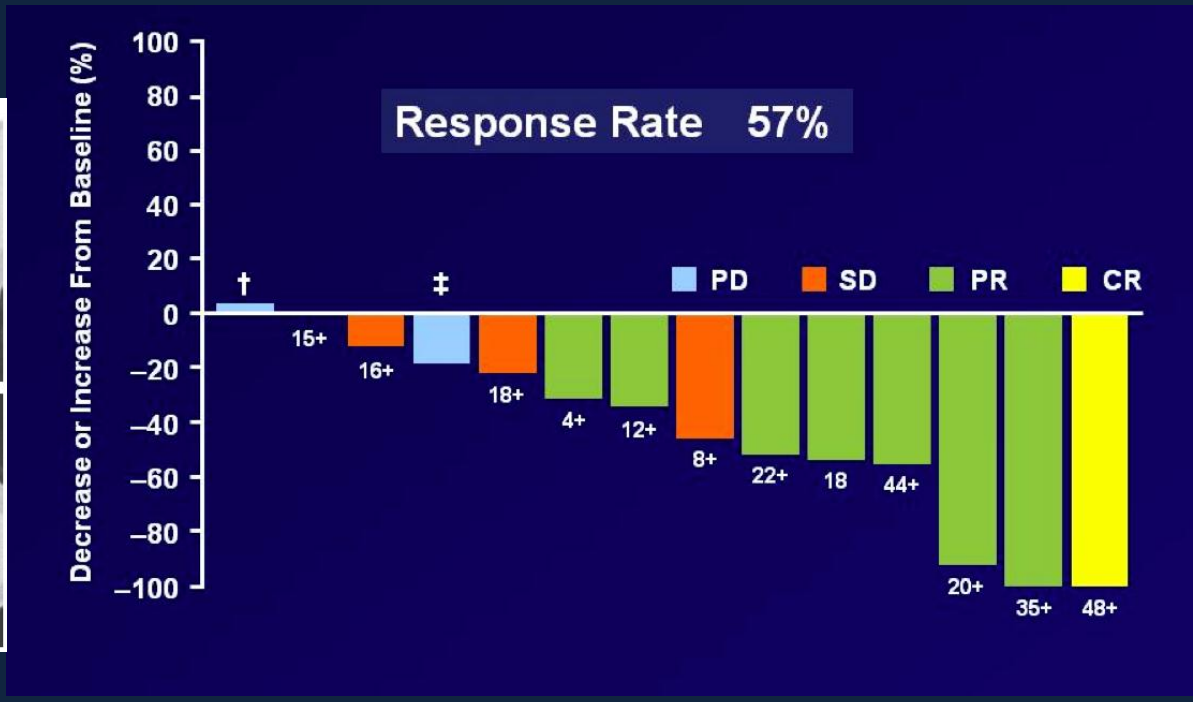


Crizotinib also inhibits ROS1

Bergethon JCO 2012; Takeuchi, Nat Med 2011

Targeting ROS (3)



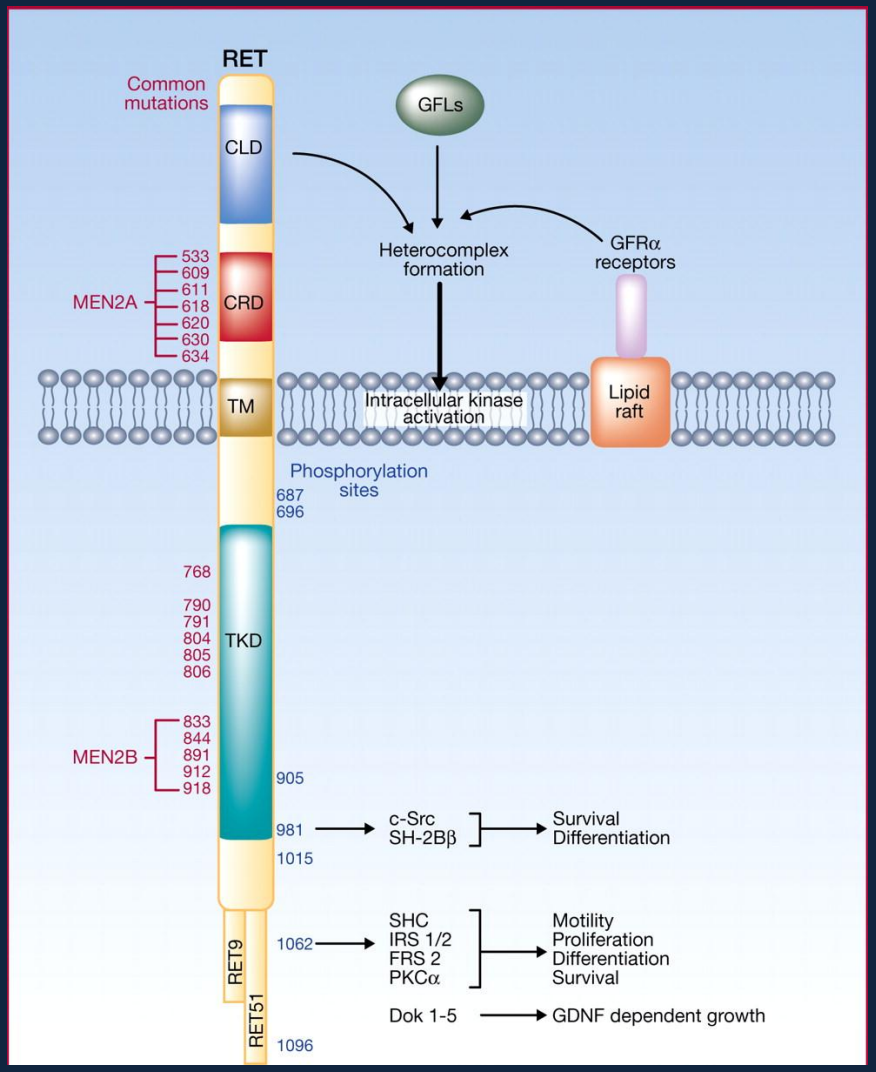


Crizotinib expansion cohort (14 patients reported)

These results validate ROS1 as a therapeutic target in lung cancer

Bergethon JCO 2012, Riely ASCO 2012; Sequist ASCO 2012

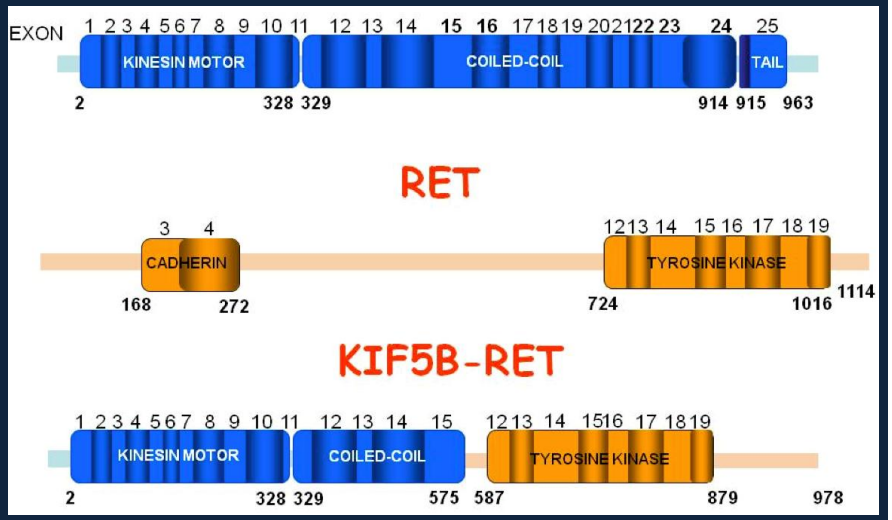
Translation in the clinic: targeting RET

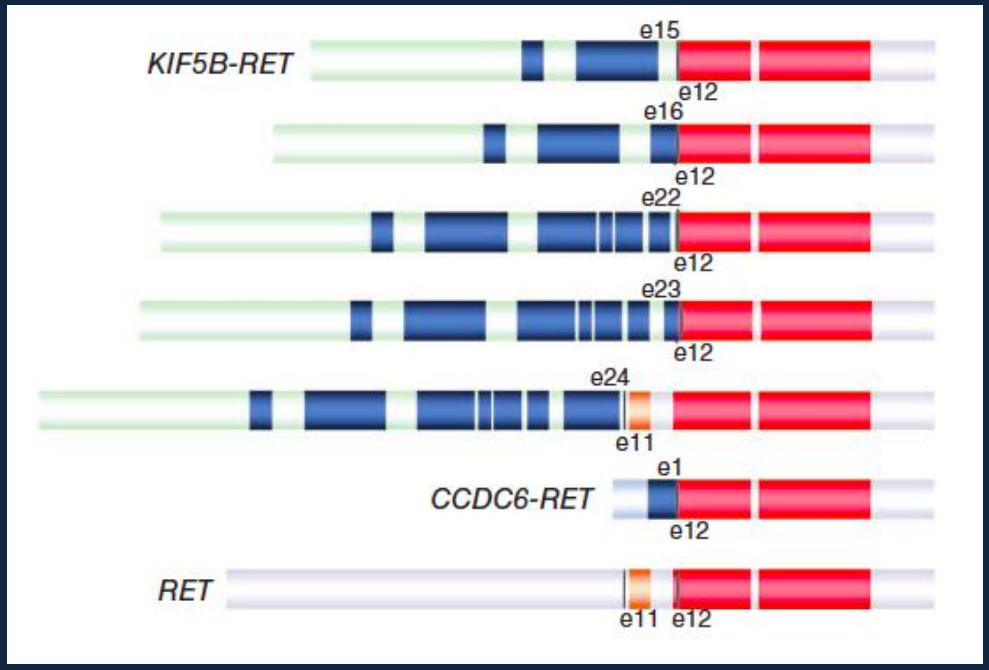


- Ligands: glial cell line-derived neurotrophic factor (GDNF) family
- Activation requires the formation of a multimere complex including the ligand, a GDNF-family receptor-α protein and RET

Phay, CCR 2010

Targeting RET (2)

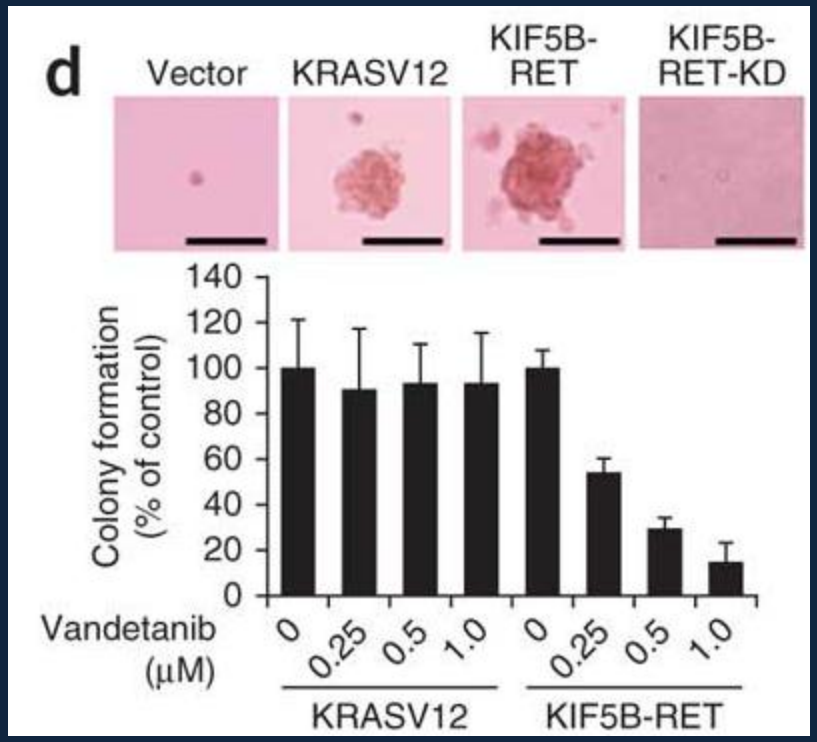


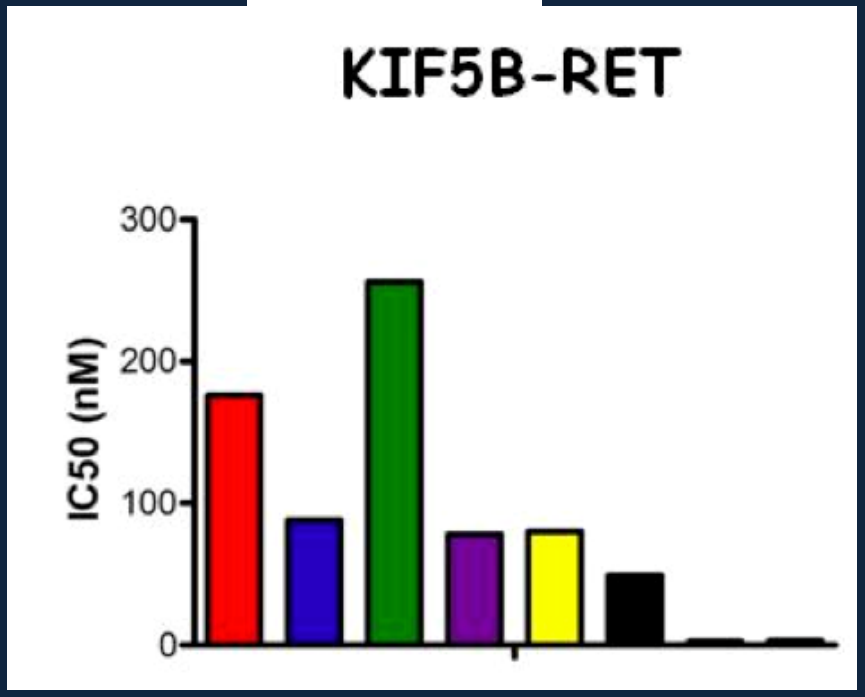


- Fusion of KIF5B and RET identified in an adenocarcinoma of a young non-smoker by whole-genome and transcriptome sequencing
- 6/319 (1.9%) RET fusion transcripts in adenocarcinoma from Japanese and 1/80 (1.3%) from Caucasian patients.

Capelletti, ASCO 2012; Young, Genome Res 2011; Kohno Nat med 2012

Targeting RET (3)





Kohno, Nat Med 2012; Capelletti, ASCO 2012

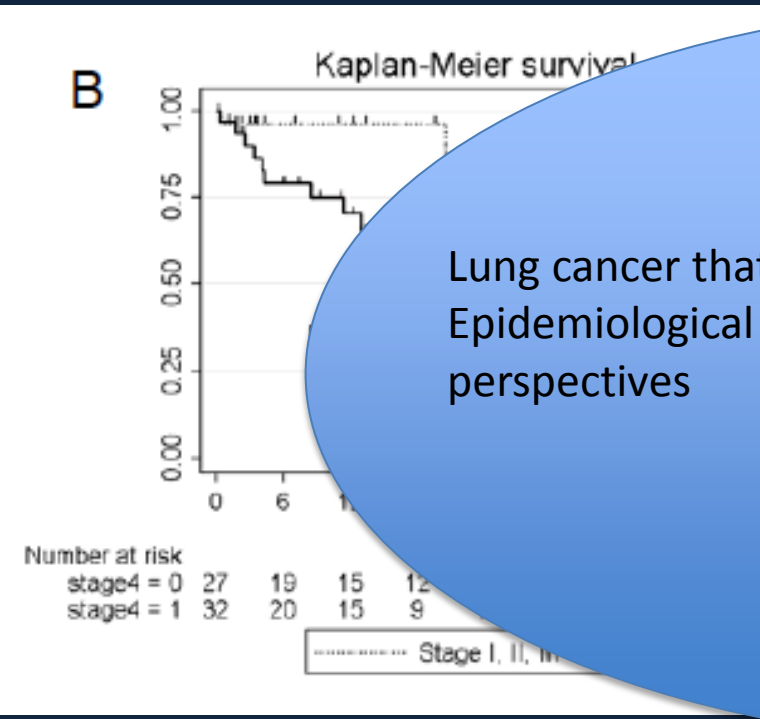
Targeting RET (4)

Study	Identification and verification method(s)	Ethnicity (n)	Percentage positive for KIF5B-RET	Variants identified
Kohno *et al.*	Whole-transcriptome sequencing[a]	Japanese (30)	3.3	K15;R12, K16;R12, K23;R12, K24;R8
	RT-PCR and Sanger sequencing	Japanese (289)	1.7	
		American (80)	1.3	
		Norwegian (34)	0.0	
	Total	**433**	**1.6**	
Lipson *et al.*	Targeted capture and resequencing[a]	Not specified (24)	4.2	K15;R11, K15;R12, K16;R12, K22;R12
	RT-PCR	Caucasian (121)	0.8	
		Korean (347)	2.2	
		Japanese (58)		
	RET IHC and RT-PCR	Caucasian (92)	1.1	
		African American (5)	0.0	
		Unknown (20)	0.0	
	Total	**667**	**1.8**	
Takeuchi *et al.*	IHC and FISH screen[a]	Japanese (1529)	**0.9**	K15;R12, K16;R12, K22;R12, K23;R12, K24;R11
Ju *et al.*	Whole-genome and whole-transcriptome sequencing[a]	Korean (1)	100.0	K15;R12, K16;R12, K23;R12
	Whole-transcriptome sequencing (screen)	Korean (5)	20.0	
	RT-PCR	Korean (15)	6.7	
	Total	**21**	**14.3**	
	Total	**2,650**	**1.3**	

No clinical validation of RET targeting

Pao, Nat Med 2012

Translation in the clinic: targeting HER2

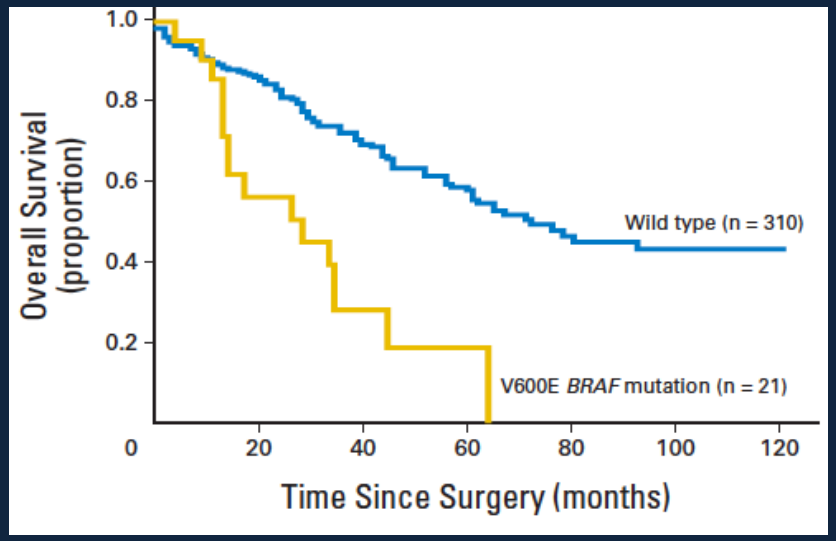


Lung cancer that harbors a HER2 mutation: Epidemiological characteristics and therapeutic perspectives

Mazières and Peters, ESM0 2012

ons in 25/1478 (6%
K negative
nt among
lated
terations
%, 24/25
patients)

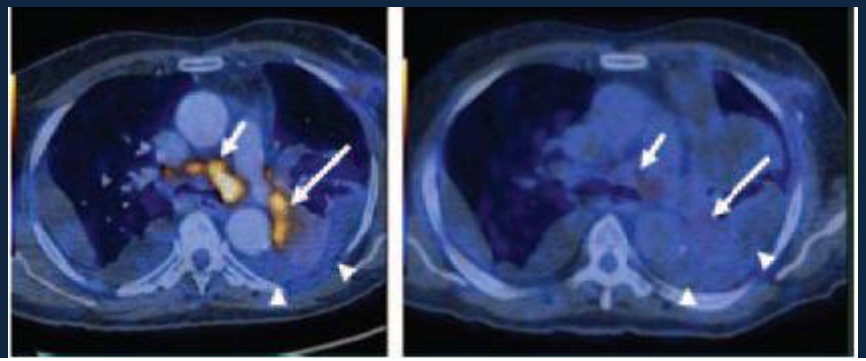
Translation in the clinic: targeting BRAF



- BRAF mutations in 36 adenocarcinoma (4.9%) and one SCC (0.3%).
- 56.8% were V600E, and 43.2% were non-V600E.
- V600E mutations were significantly more prevalent in females and an aggressive micropapillary subtype with shorter disease-free and overall survival rate.

Marchetti, JCO 2012

Targeting BRAF (2)



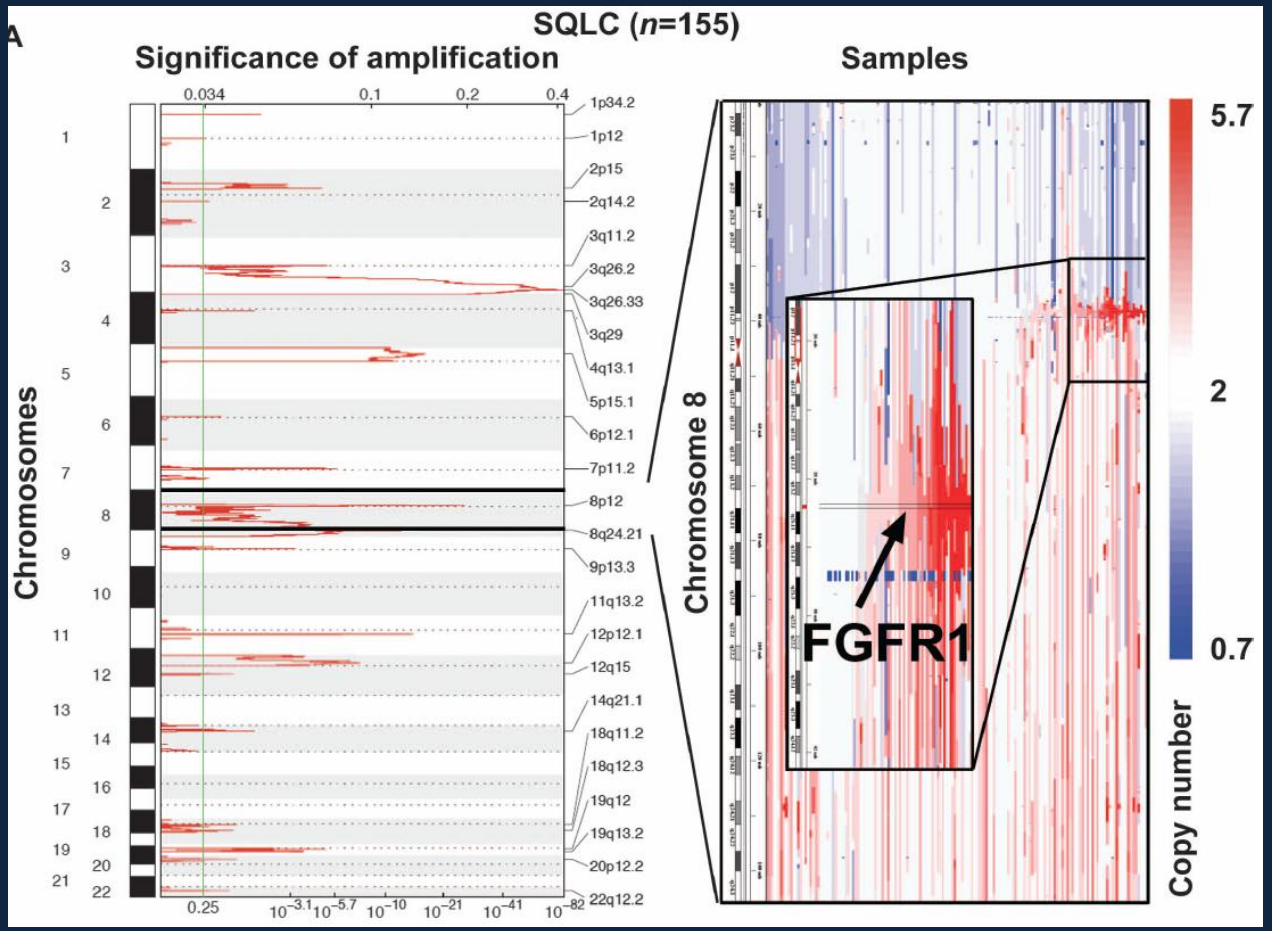
A Patient With BRAF V600E Lung Adenocarcinoma Responding to Vemurafenib

Kinase-Impaired *BRAF* Mutations in Lung Cancer Confer Sensitivity to Dasatinib

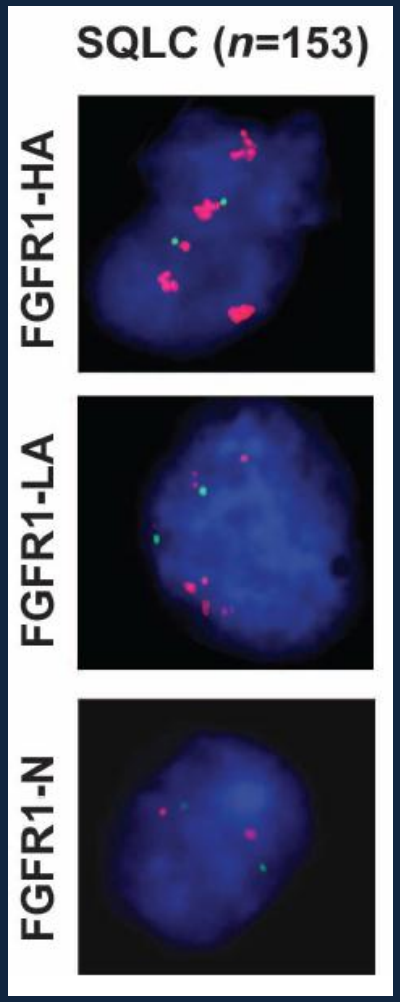
Banibrata Sen,[1*] Shaohua Peng,[1*] Ximing Tang,[1] Heidi S. Erickson,[1] Hector Galindo,[1,2,3] Tuhina Mazumdar,[1] David J. Stewart,[1] Ignacio Wistuba,[1,2] Faye M. Johnson[1,4†]

Gautschi, JTO 2012; Solit and Janne Nature 2012; Sen, Sci Transl Med 2012

Translation in the clinic: targeting FGFR1



SNP Array: ~10% of SCC Amplification



FISH ~22% of SCC Amplification

Weiss, Sci Transl Med. 2010

Targeting FGFR1 (2)

Some examples in early clinical trials:

AP24534 (Ponatinib) - BCR/ABL, PDGFR, VEGFR, FGFR

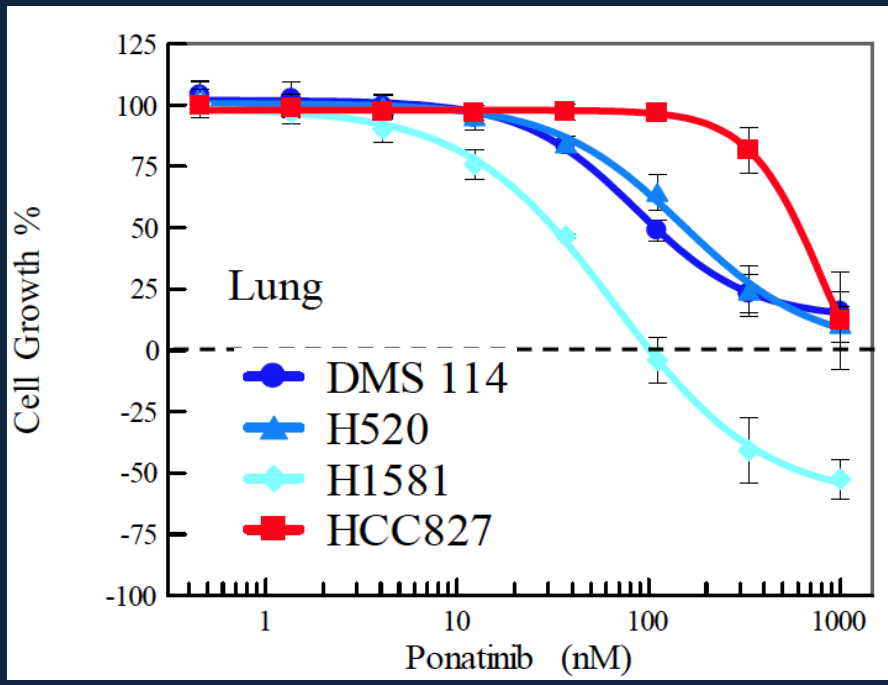
AZD4547 - FGFR, VEGFR, PDGFR

GJ398 – FGFR

BIBF1120 (Intedanib) - VEGFR, PDGFR, FGFR

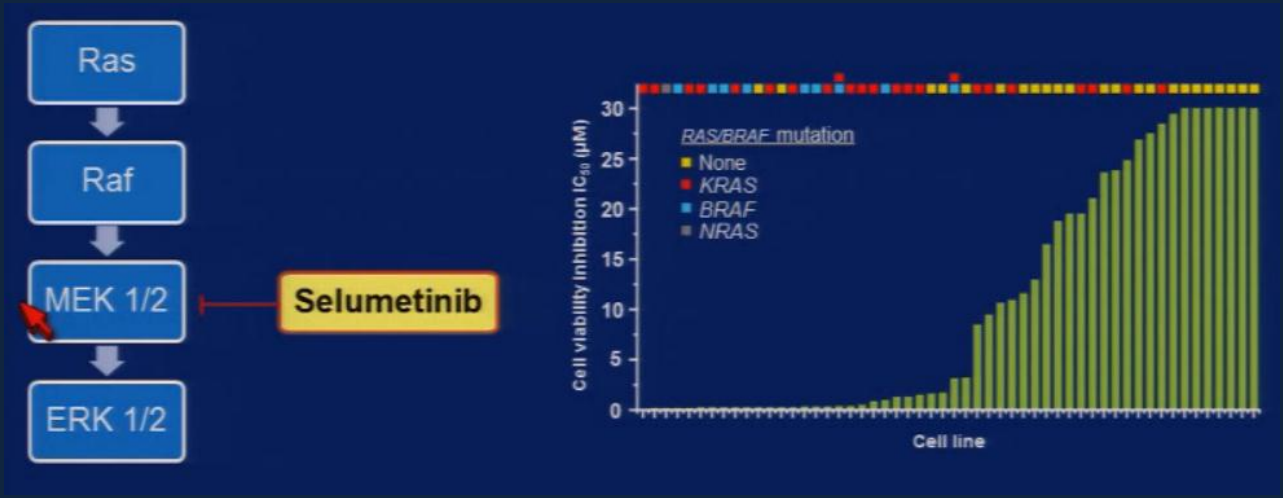
TKI258 (Dovitinib) - FLT3, c-KIT, FGFR, VEGFR

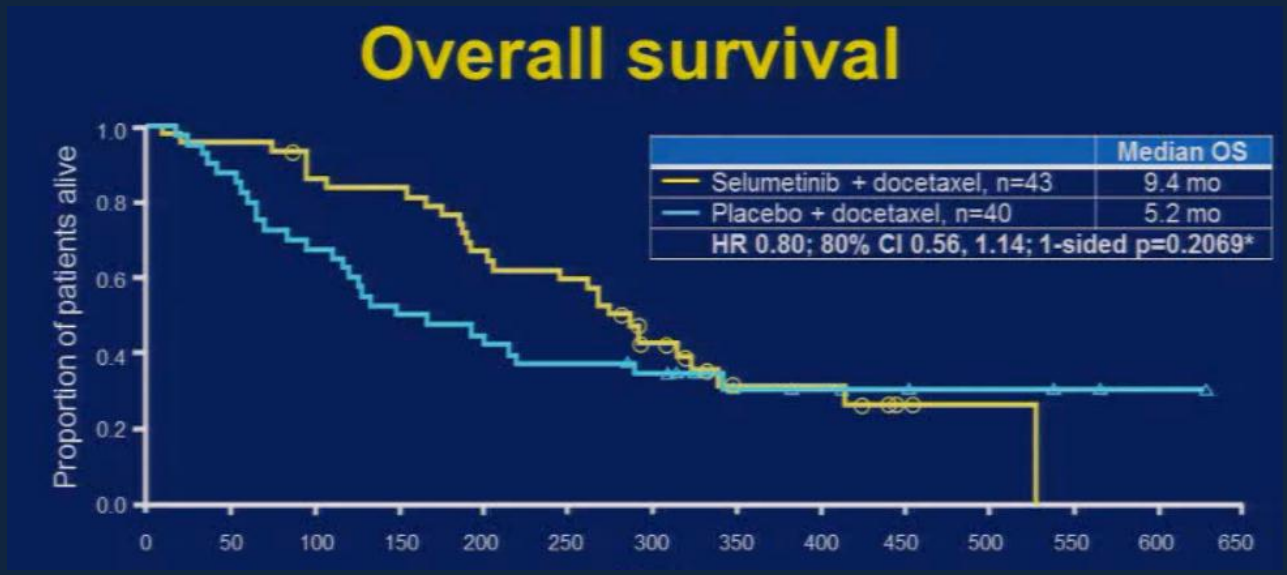
PD173074 - FGFR, VEGFR



Gozgit, Mol Cancer Ther 2012;
Weiss, Sci Transl Med. 2010

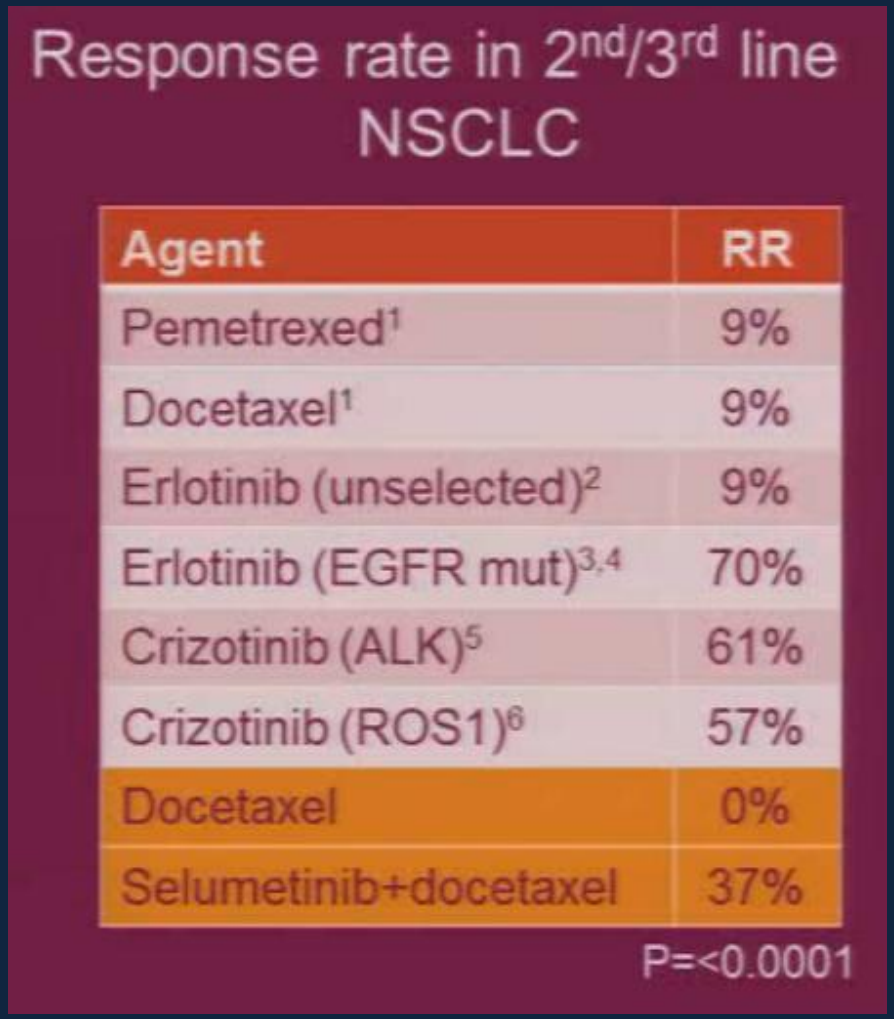
Translation in the clinic: targeting KRAS pathway





Janne, ASCO 2012

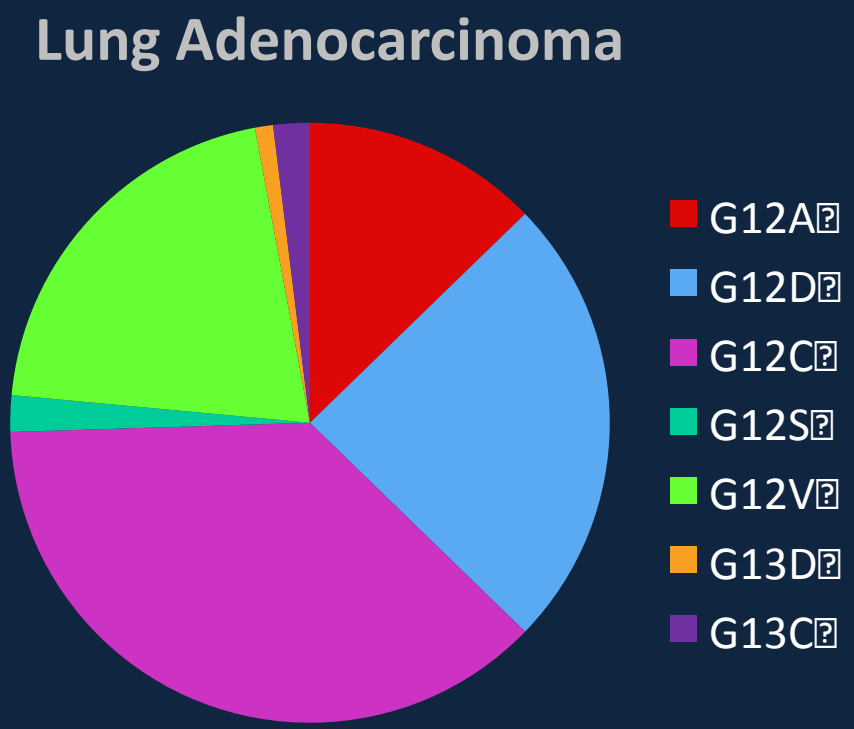
Targeting KRAS pathway (2)



Janne, Neal ASCO 2012

Targeting KRAS pathway (3)

Types of *KRAS* mutations



Hainsworth, Clin Cancer Res 2008

Targeting KRAS pathway (4)

KRAS G12 mutation frequencies

CRC

NSCLC

COSMIC

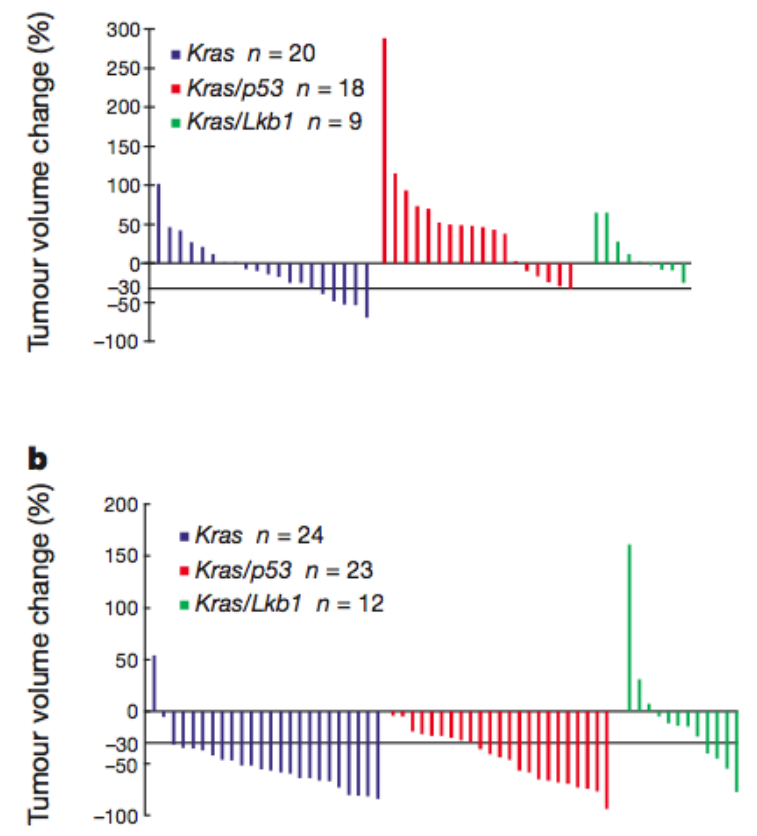
G12A G12C G12D G12E G12F G12W

G12L G12R G12S G12V G12W G12Y

RAS mutations and oncogenesis: Not all RAS mutations are created equally
Miller & Miller (2011) Front Genet 2:100

Targeting KRAS pathway (5)
A new stategy

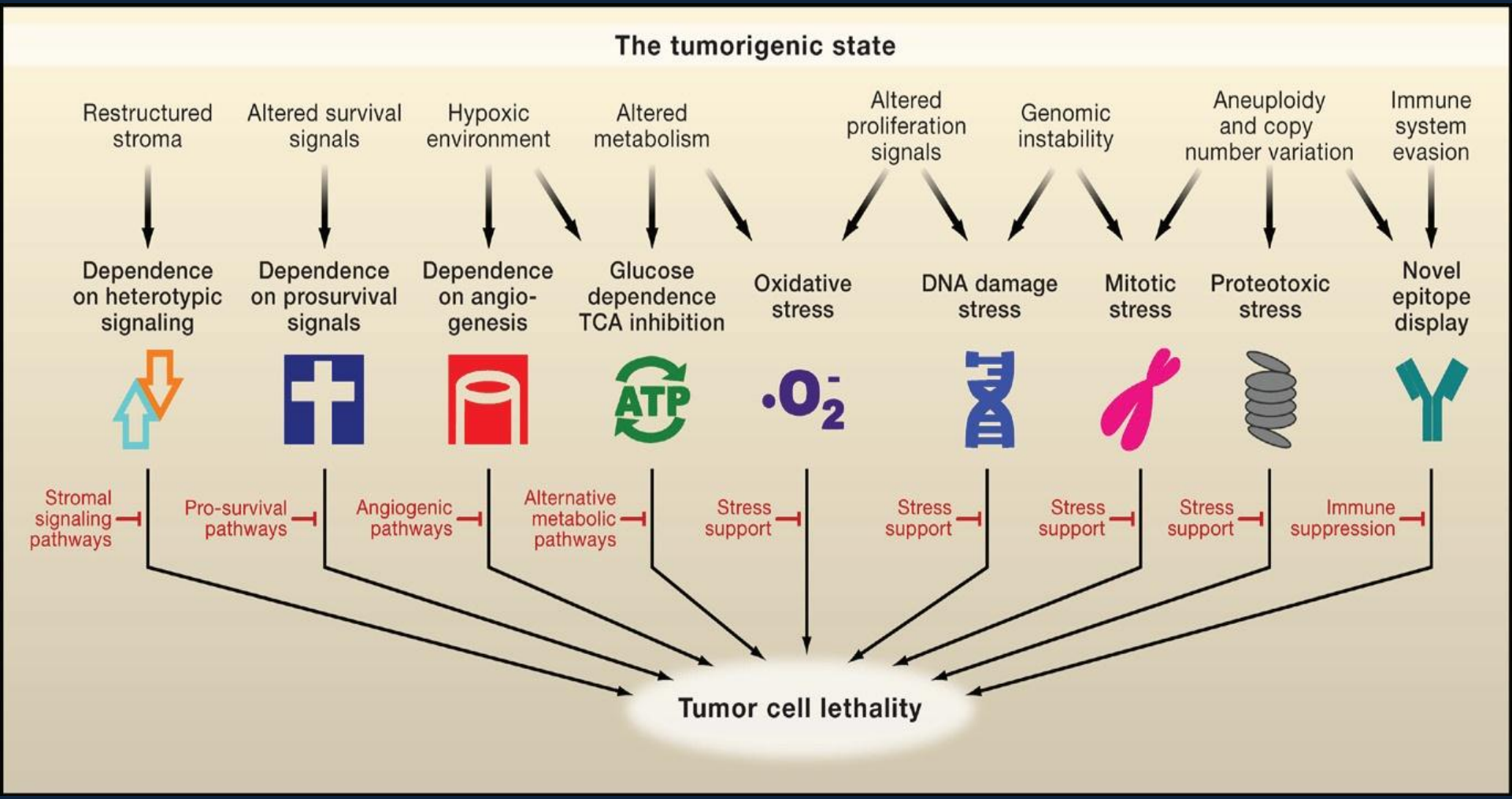
A murine lung cancer co–clinical trial identifies genetic modifiers of therapeutic response



Co-clinical results identify predictive genetic biomarkers that should be validated by interrogating samples from patients enrolled on the concurrent clinical trial, allowing to to anticipate the results and generate clinically relevant hypotheses.

Chen, Nature 2012

Cancer Cell Can Survives in a Hostile Environment



Luo, Cell 2009

Conclusions

Everything has become largely more complex

PERSPECTIVES:

- For almost every single indentified driver, early trials with targeted agent are ongoing (phase I/II)
- The “NSCLC”-devoted trial will probably become a rare concept in the years to come
- Prospective molecularly-driven trials will require large international network of centers, political and economical support as well as a strong multidisciplinary collaboration

Thanks for your attention