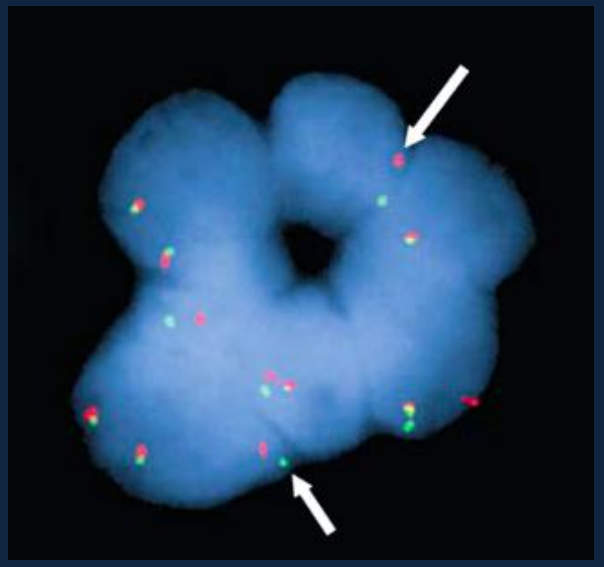


Molecular Typing of Lung Cancer: More pieces to the puzzle

Dr Solange Peters, MD-PhD

Cancer Center

Lausanne-Switzerland

Disclosures

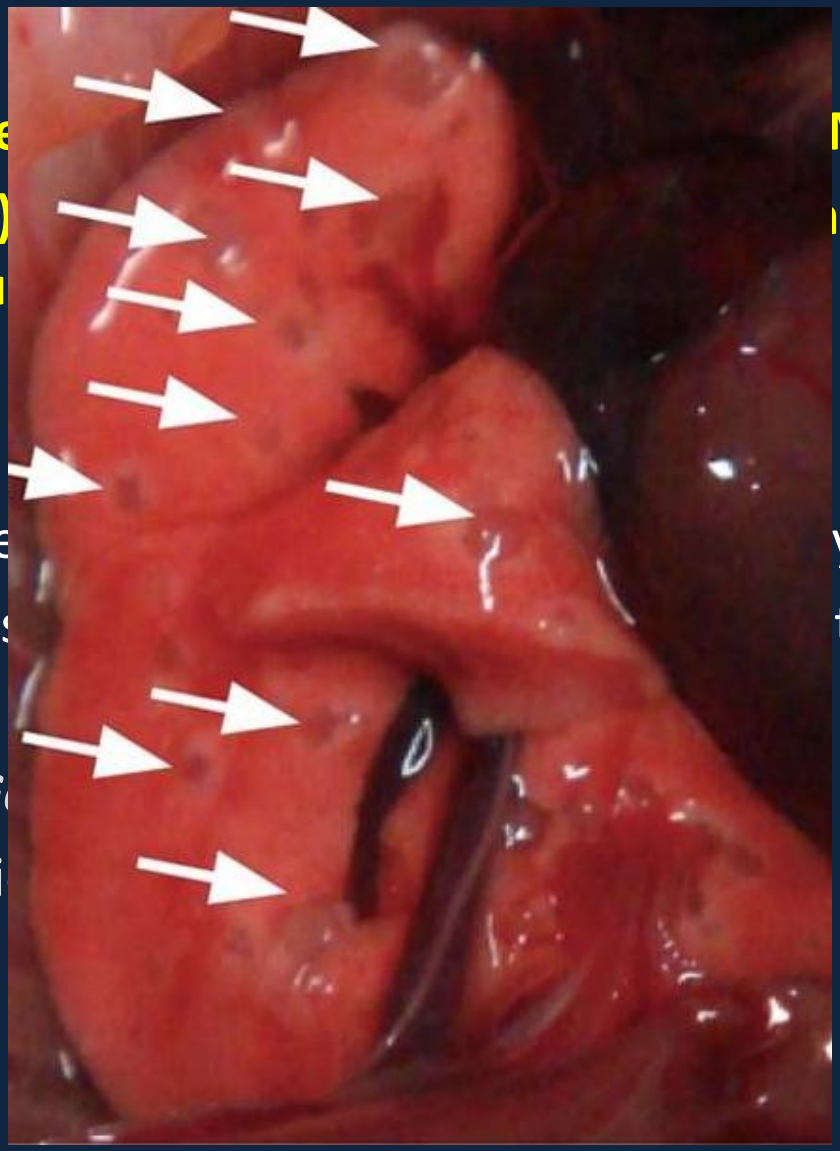
I have provided consultation, attended advisory boards and/or provided lectures for:

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.

Cancer genome and driver genes

- ✧ **3142 gene** **MIC database)**
- ✧ **10% (286)** **ncogenes, 90% tumour su**



Oncogenes

- – About 33 gene **y**
- – By definition, **t tumors**

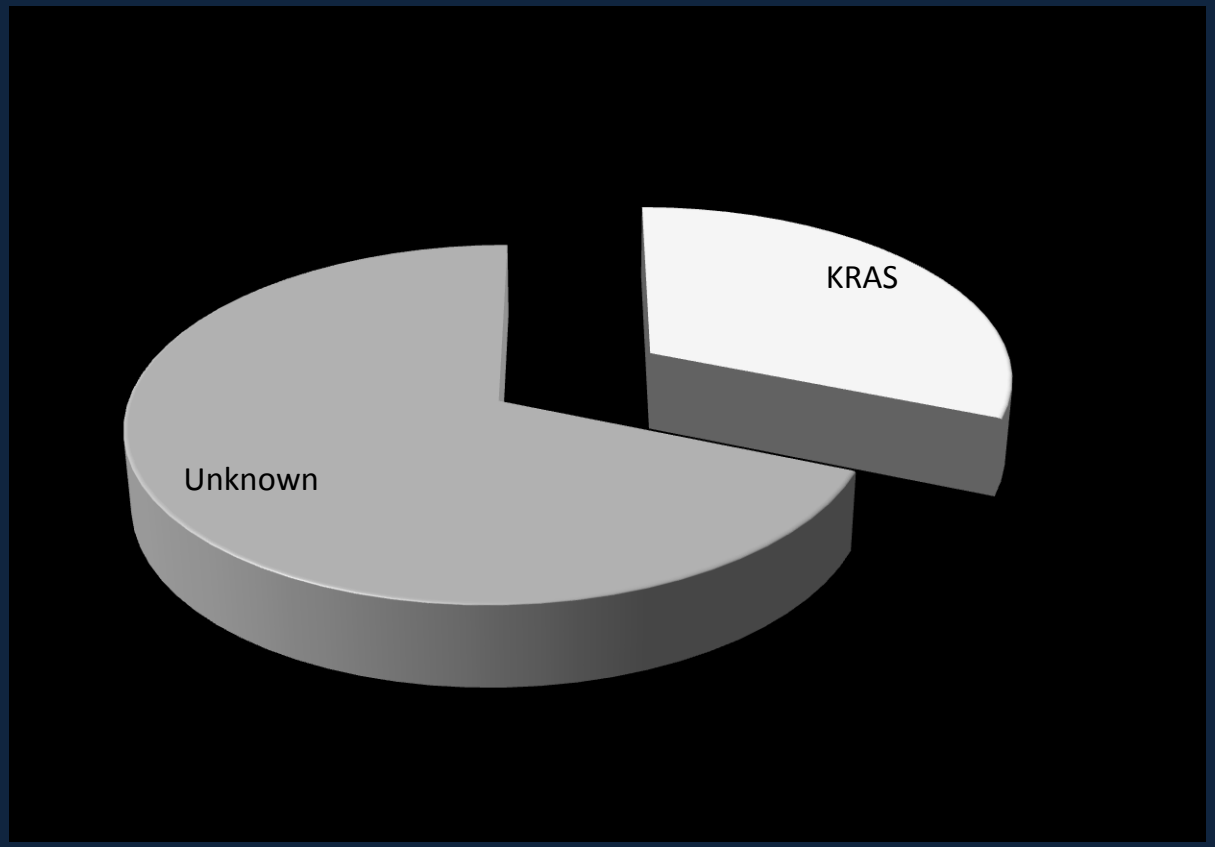
Tumor Suppressor G

- – 15% of mutati
- – Cannot be inh

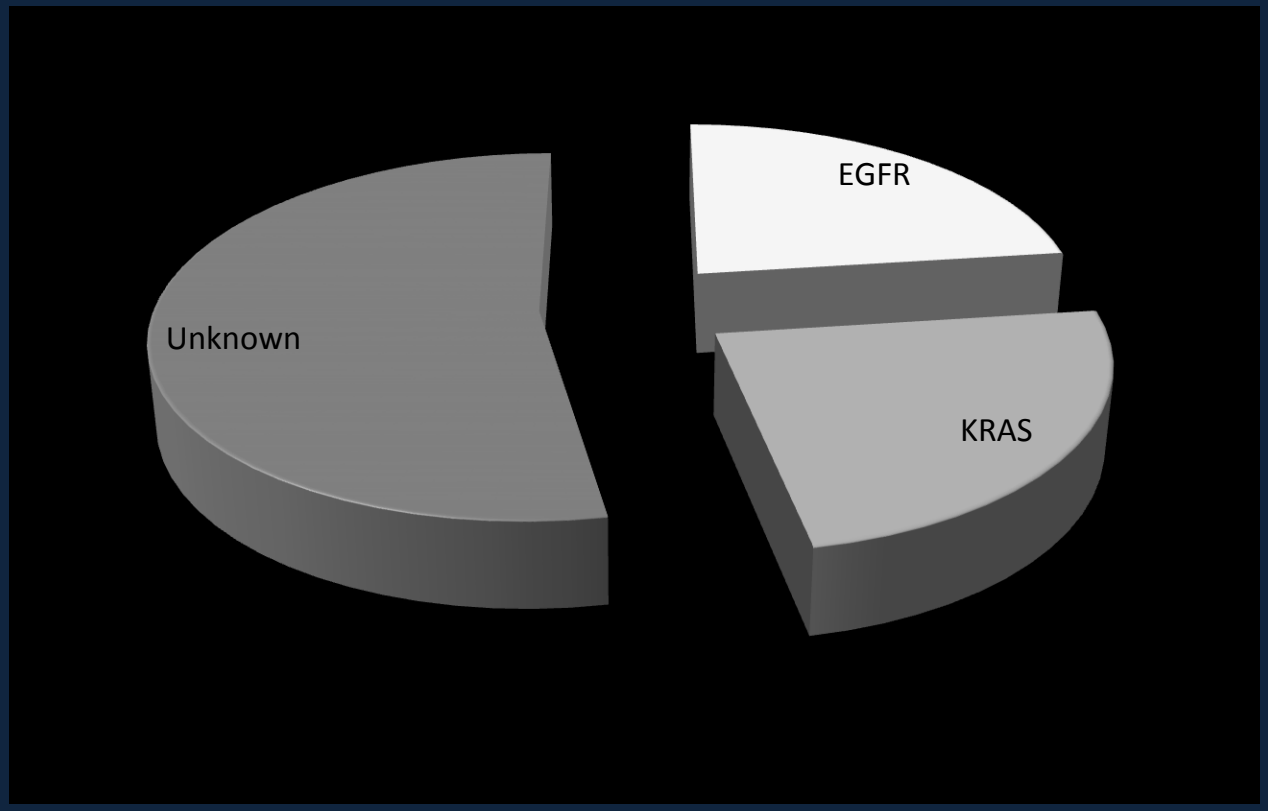
Core mutated pathways

PI3K/mTOR	Control of G1S	Jak-Stat
DNA damage control	TGF β	Notch
WNT	KRAS	Apoptosis
Cell adhesion	HIF1α	Hedgehog

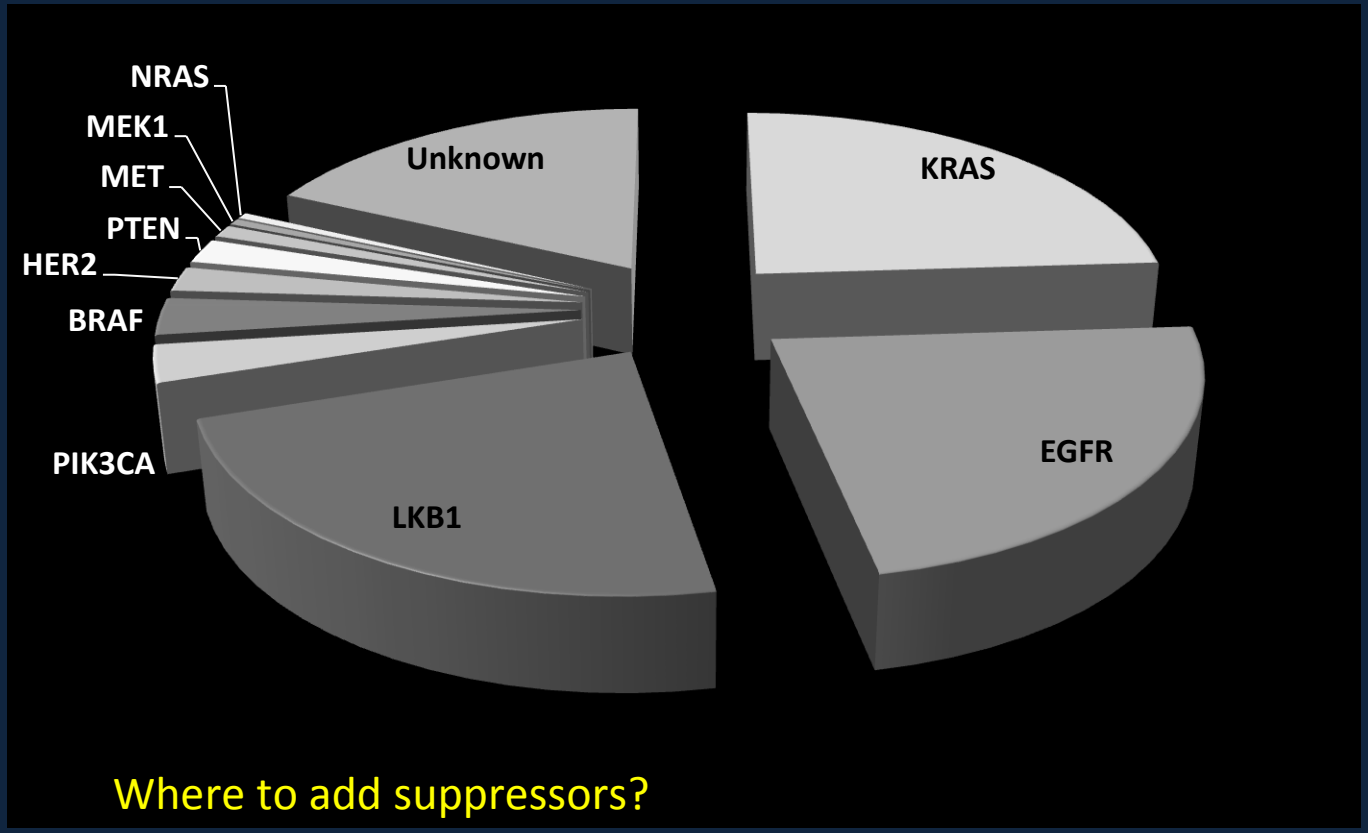
Adenocarcinoma driver mutations: 1990



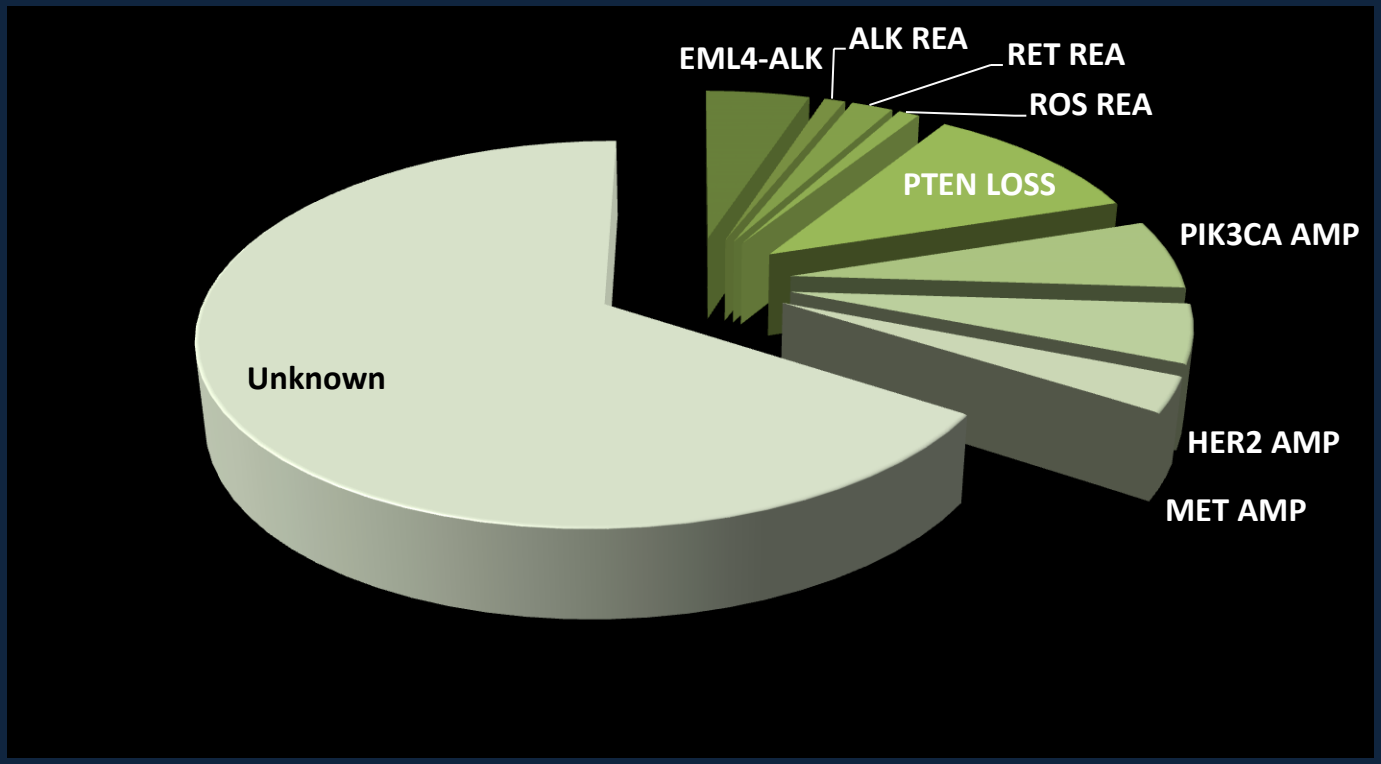
Adenocarcinoma driver mutations 2004-2008



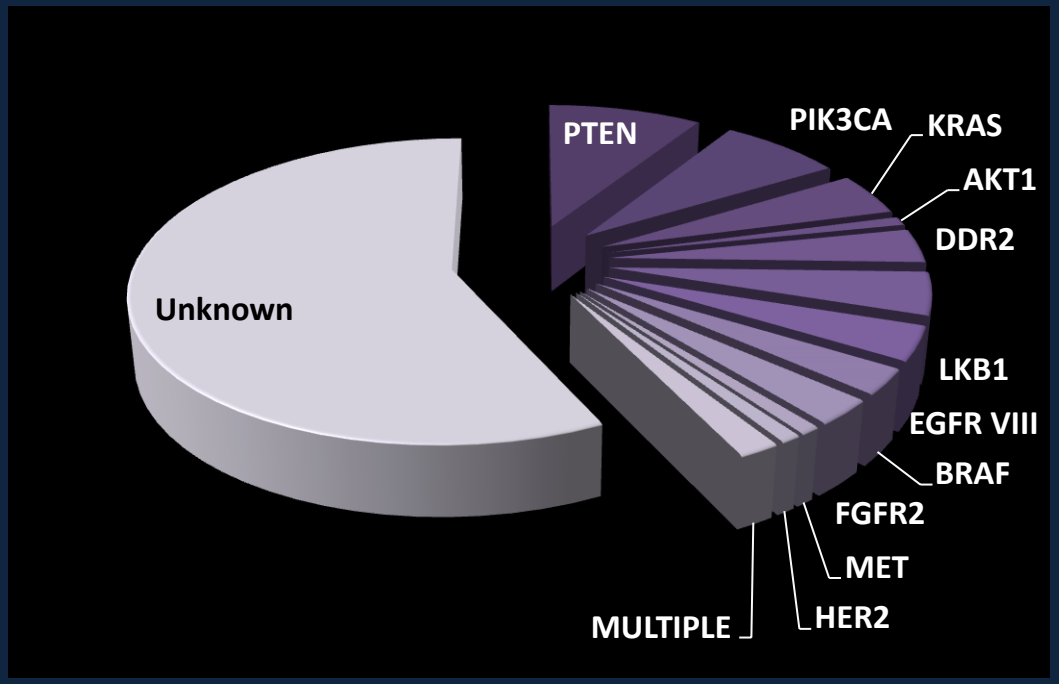
2012 update on adenocarcinoma driver mutations

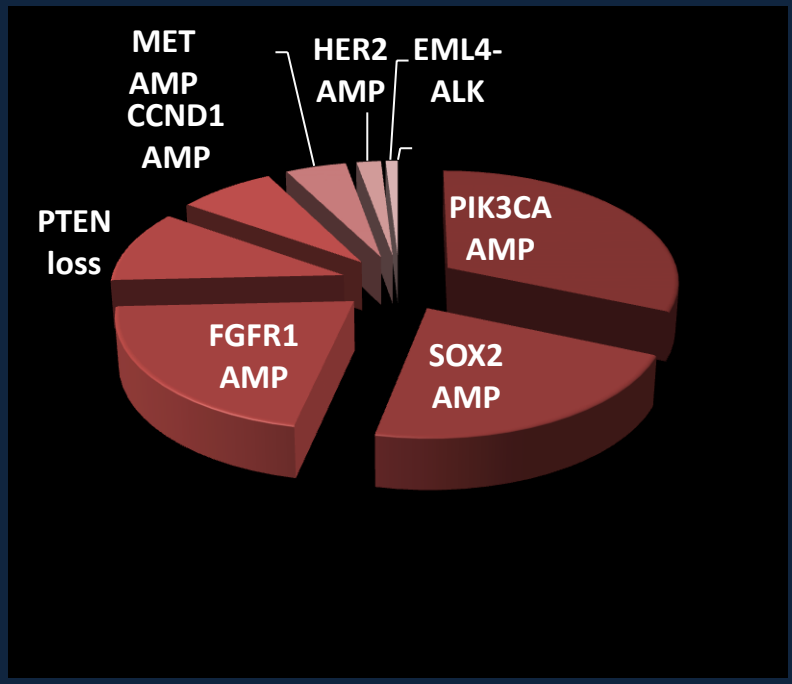


2012 update on adenocarcinoma « quantitative » gene alterations



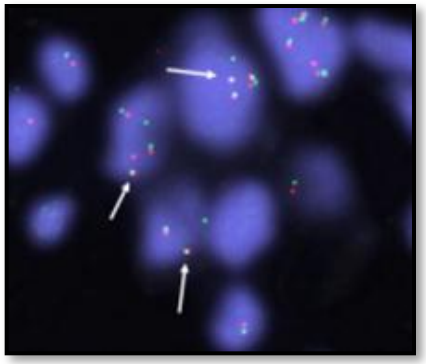
Update on squamous carcinoma driver mutations/ « quantitative » alterations





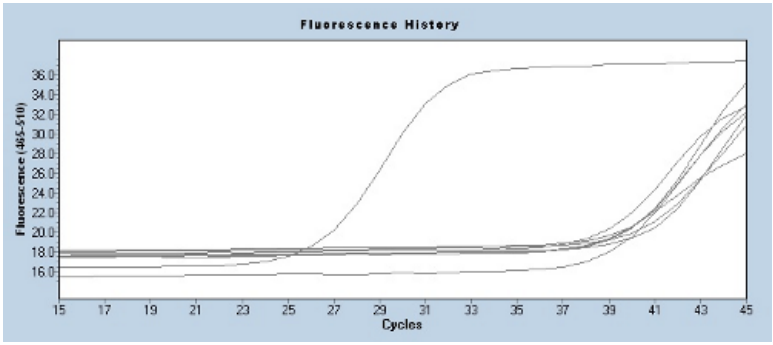
Prez-Moreno, CCR 2012; Paik, ASCO 2012, TCGA, Nature 2012

Methods of predictive marker testing



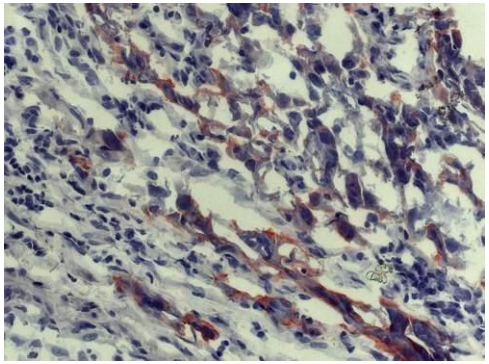
Fluorescence In Situ Hybridization (FISH)

Method for the detection of presence or absence of DNA sequences on chromosomes



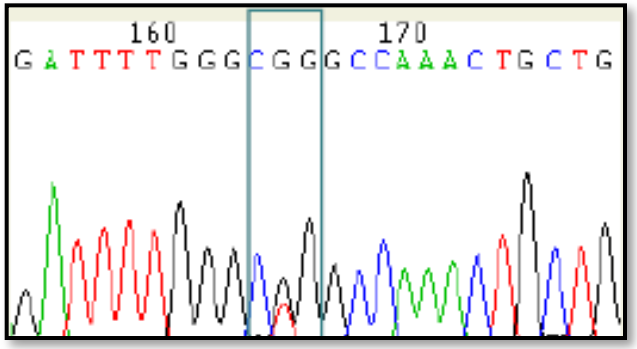
Real Time Polymerase Chain Reaction (PCR)

Amplification of DNA followed by use of probes to detect specific sequences



Immuno-histochemistry (IHC)

Targeting of marker-linked antibodies against cell component of interest (e.g. ALK translocation)

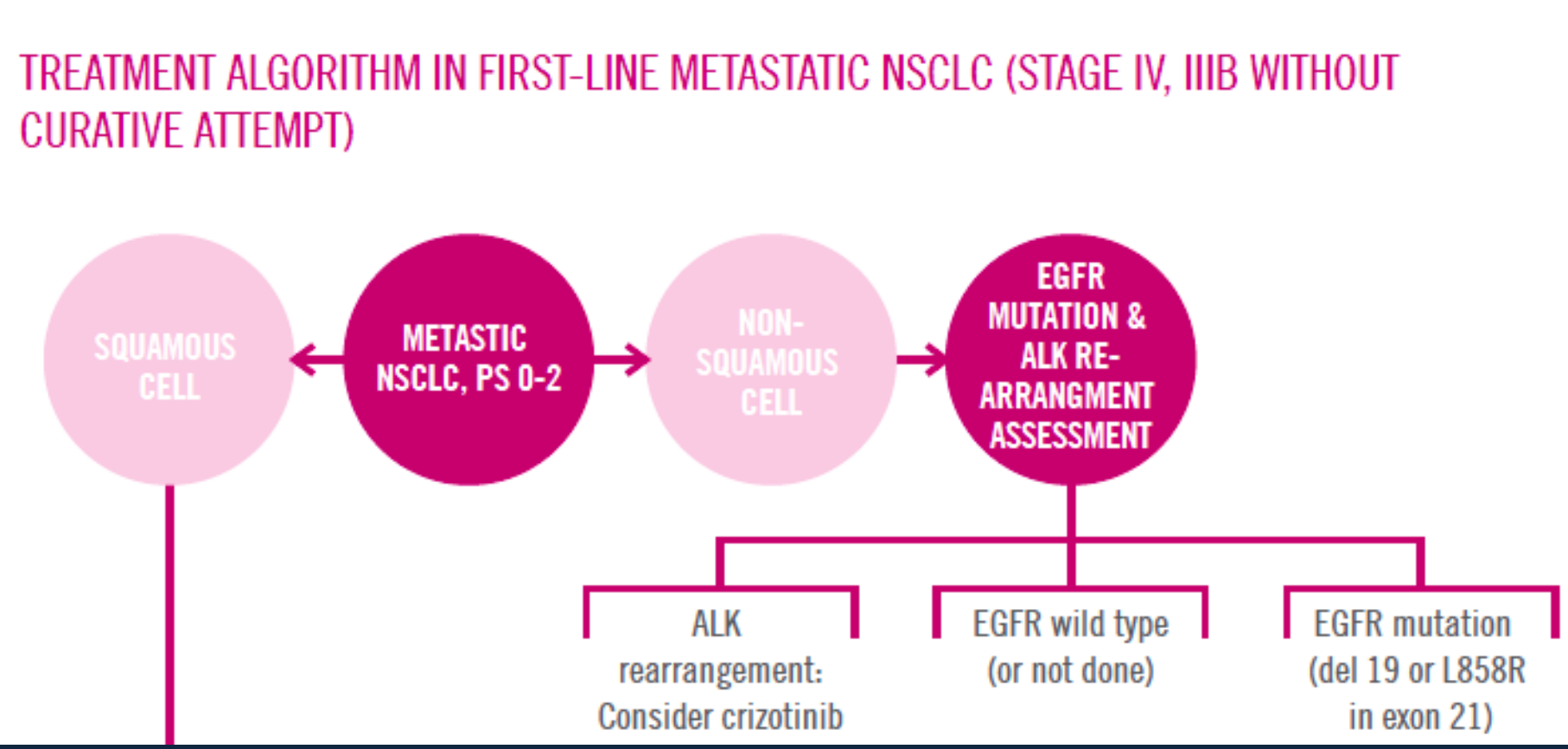


DNA Sequencing

One of several sequencing techniques to identify variations from wild type control sequence

Molecular standards in NSCLC

Minimal testing



Peters et al, Ann Oncol 2012

Molecular pathology of NSCLC

More pieces TO THE PUZZLE

3 PIECES OF THIS PUZZLE:

- EGFR
- ALK
- MET

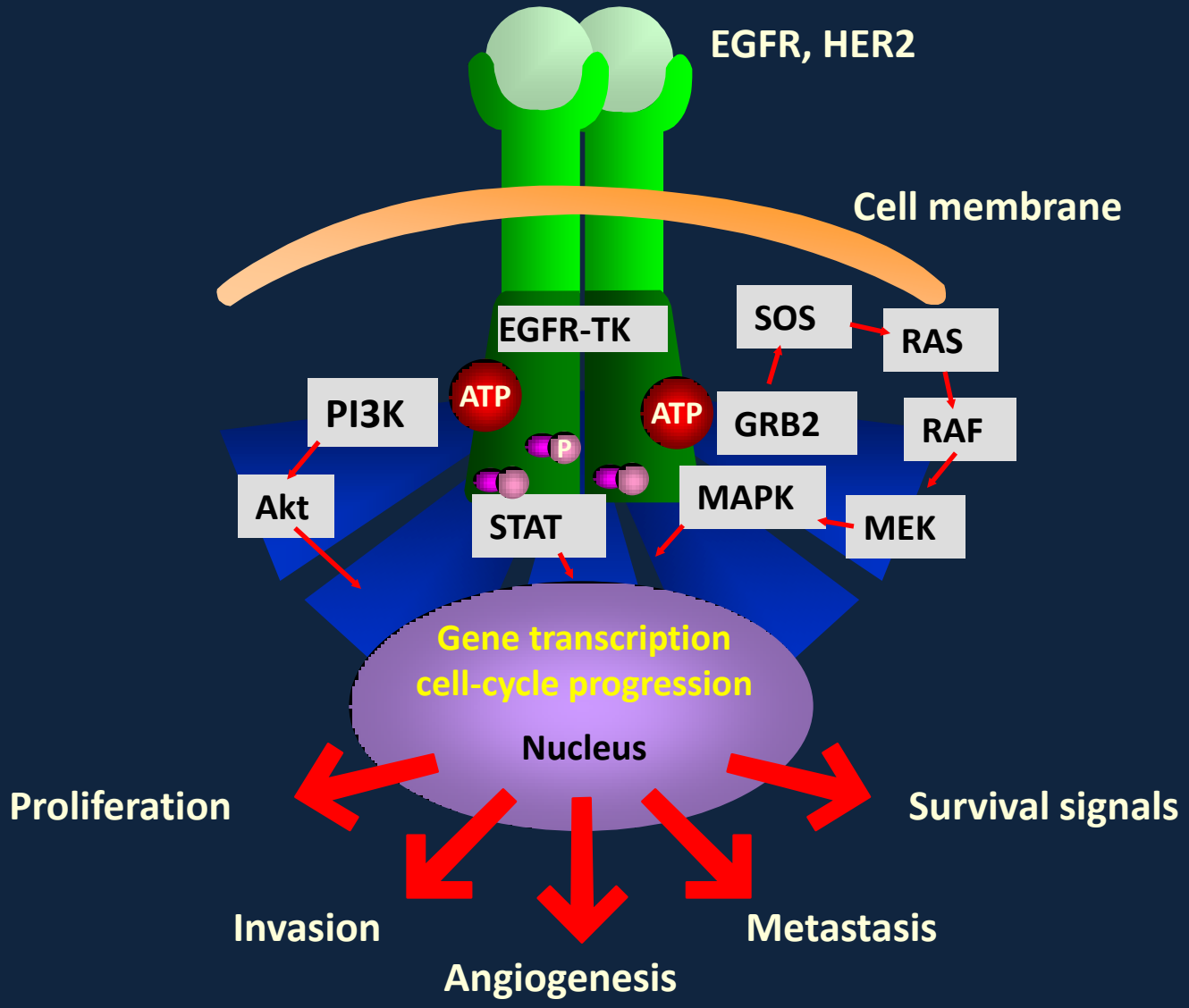
Molecular pathology of NSCLC

More pieces TO THE PUZZLE

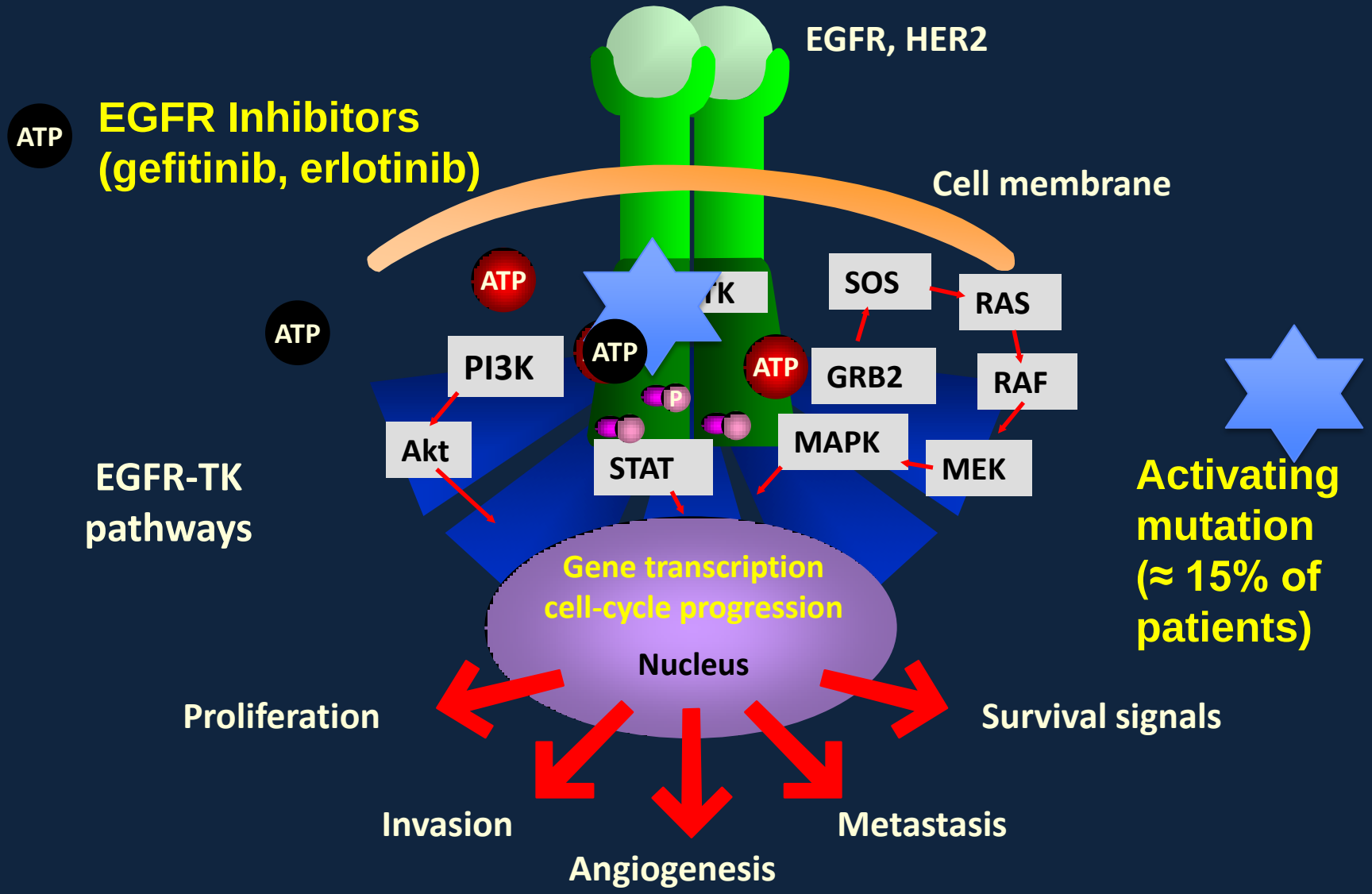
3 PIECES OF THIS PUZZLE:

- **EGFR: high level of evidence and knowledge**
- ALK
- MET

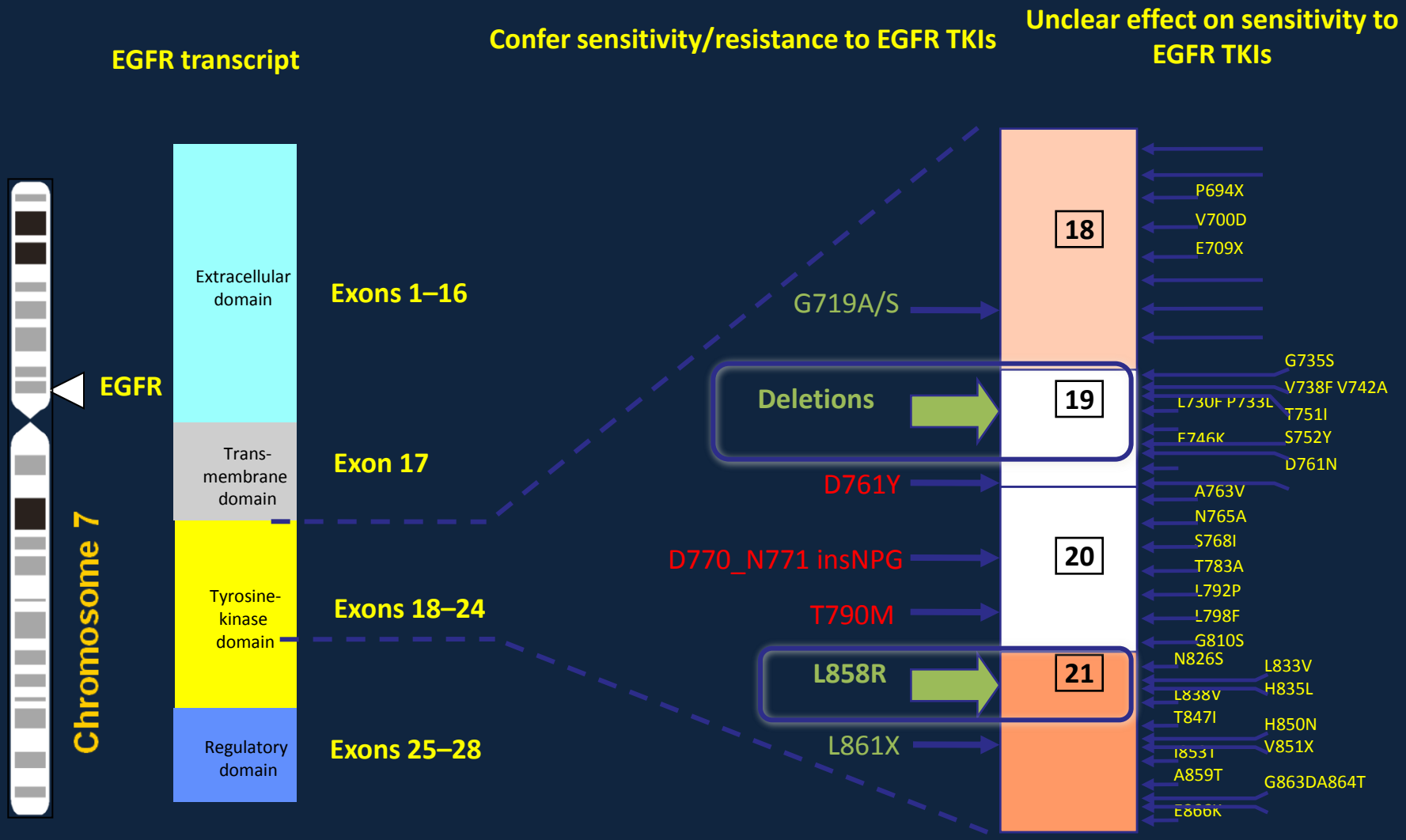
Epidermal growth factor receptor (EGFR) signaling pathway (1980)



Inhibition of EGFR signaling pathway with activating mutation (2004)



Mutations in the *EGFR* gene



Riely, Clin Cancer Res 2006

Sensitivity to EGFR-TKI according to different EGFR mutations

N	EGFR	RR (%)	PFS (months)	OS (months)
278	Classical exon 19-21	74.1	8.5	19.6
272	Wild-type	16.5	2.0	10.4
11	Exon 20 insertion	0	1.4	4.8
15	G719	53.3	8.1	16.4
15	L861	60.0	6.0	15.2
15	Uncommon mutations	20.0	1.6	11.1

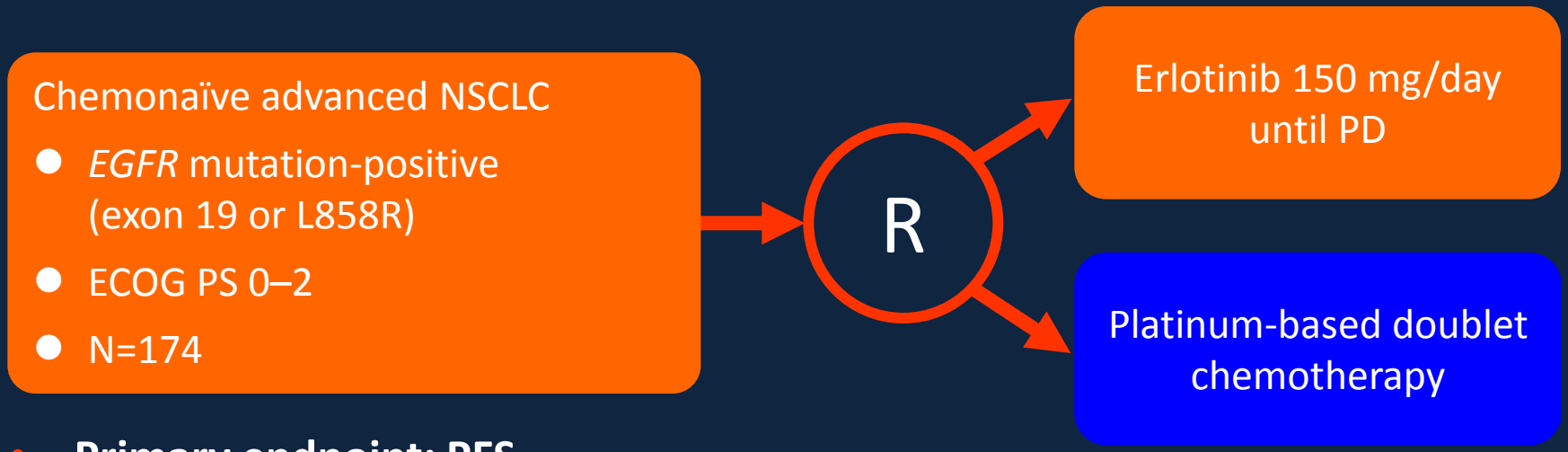
Wu, Clin Cancer Res 2011

Studies of EGFR TKIs versus chemotherapy as first-line therapy in EGFR Act Mut+ NSCLC

Study	EGFR TKI	n	Median PFS in TKI arm (months)	P value	HR
OPTIMAL	Erlotinib	154	13.1	<0.0001	0.16
First Signal	Gefitinib	42	8.4	0.084	0.61
IPASS	Gefitinib	261	9.5	<0.0001	0.48
WJTOG 3405	Gefitinib	177	9.2	<0.001	0.48
NEJSG 002	Gefitinib	200	10.8	<0.001	0.36
EURTAC	Erlotinib	174	9.4	<0.0001	0.42
LUX-3	Afatinib	308	13.6	<0.0001	0.47

EURTAC: erlotinib first-line in *EGFR* mutation+ NSCLC

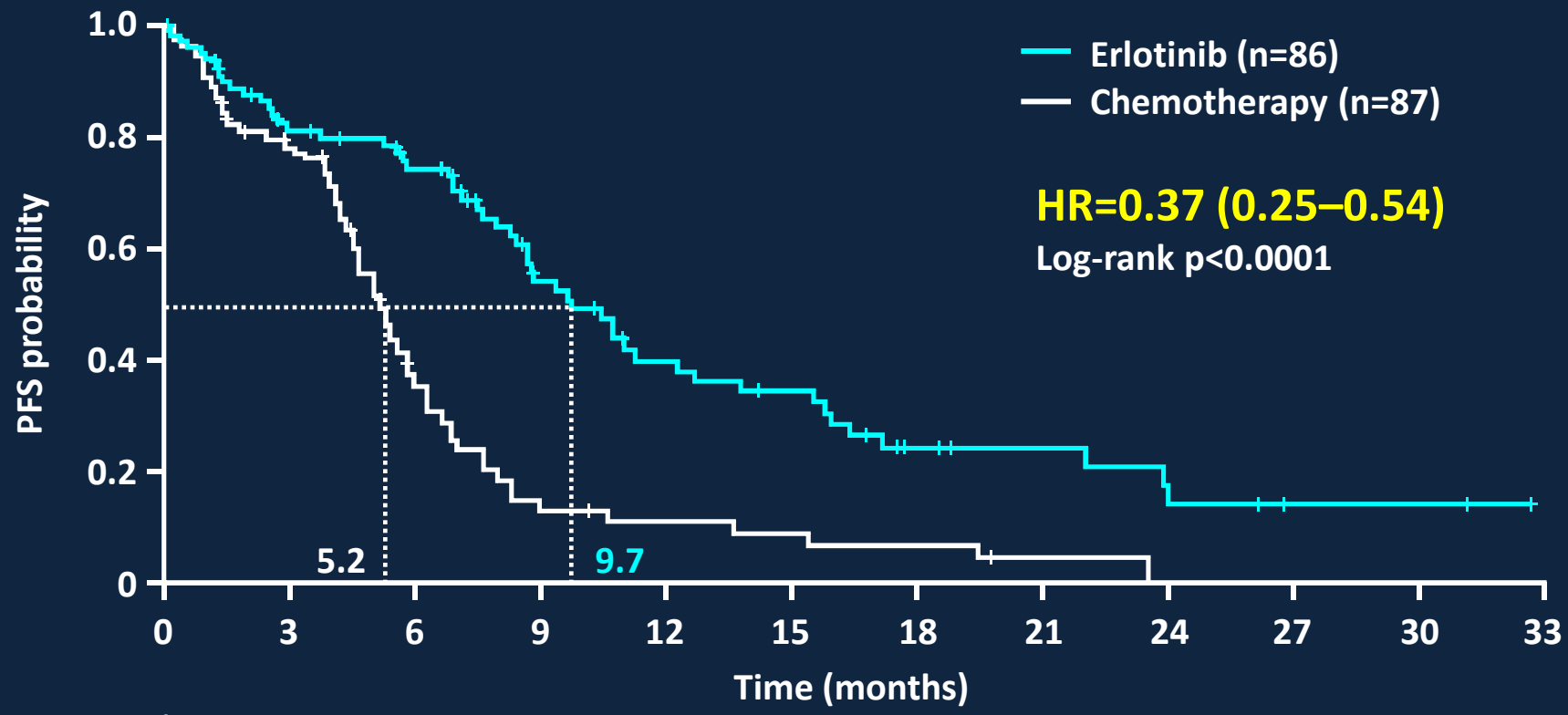
- Phase III study initiated by the Spanish Lung Cancer Group (GECP)
- Recruitment in Spain, Italy and France



- **Primary endpoint: PFS**
- **Secondary endpoints: ORR, 1-year survival, OS, safety, QoL, localisation of PD**

ORR = objective response rate; QoL = quality of life

EURTAC: PFS in ITT population



Patients at risk

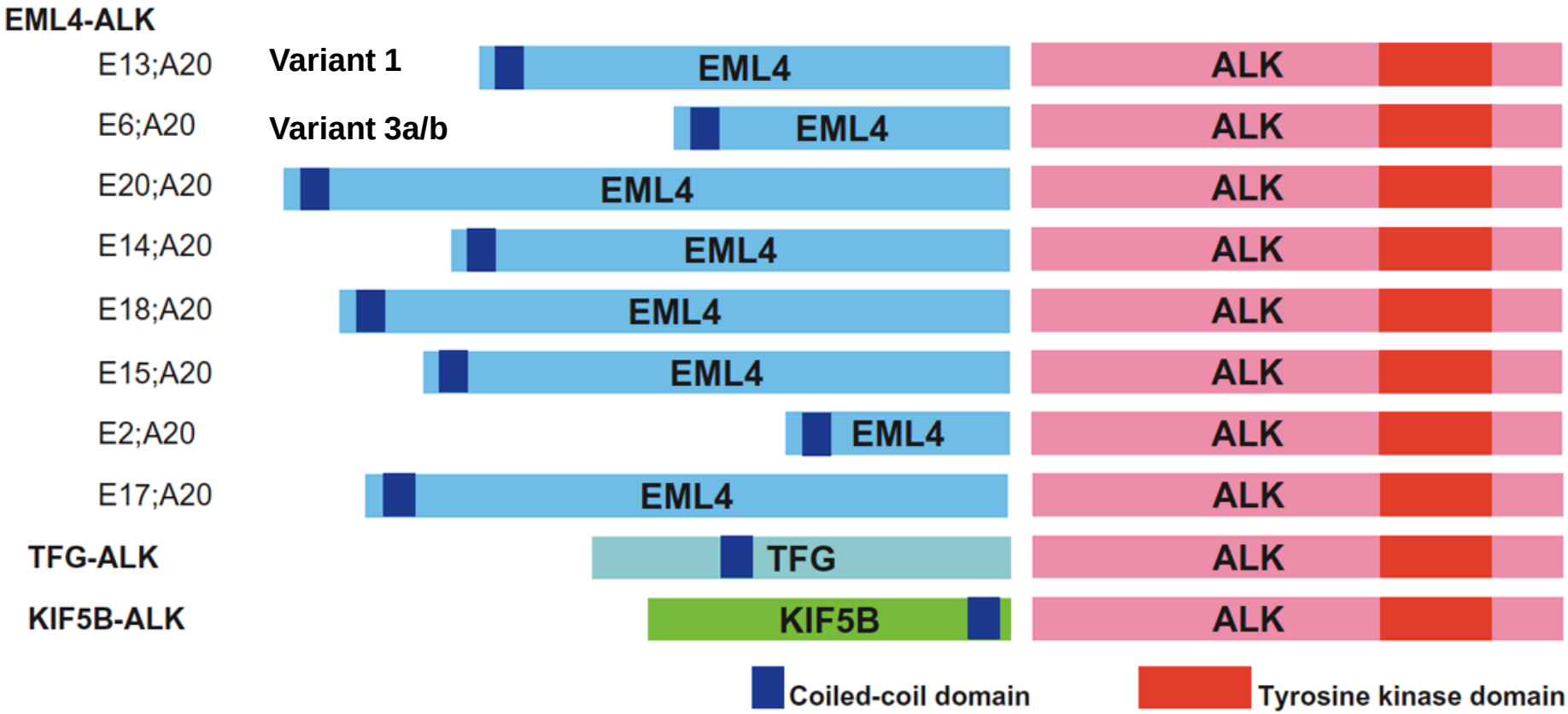
Erlotinib	86	63	54	32	21	17	9	7	4	2	2	0
Chemo	87	49	20	8	5	4	3	1	0	0	0	0

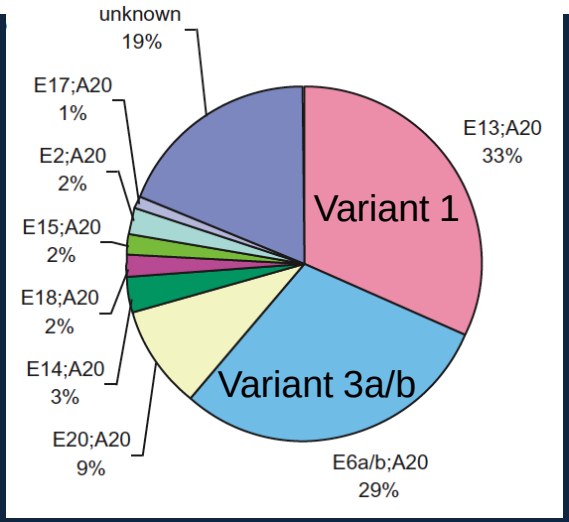
Molecular pathology of NSCLC

More pieces TO THE PUZZLE

3 PIECES OF THIS PUZZLE:

- EGFR: high level of evidence and knowledge
- **ALK: growing level of evidence and knowledge**
  - Standard testing method
  - ALK + demographics
  - Molecular biology characteristics
  - (Benefit vs chemotherapy)
- MET





Eur J Cancer 2010

Detection of ALK rearrangements

- Fluorescence in situ Hybridization (FISH)
- Immunohistochemistry (IHC)
- Revers transcriptase PCR (RT-PCR)

Translation in the clinic: targeting ALK

Prevalence in NSCLC: Retrospective Data

	RT-PCR	FISH	IHC
% ALK+ patients Unselected	1.6% - 4.9%	2.7%- 4.2%	1.7% - 8.6%
% ALK+ patients Adenocarcinoma	2.4% - 4.9%	5.6%	2.7%

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

Vysis ALK Break Apart FISH Probe Kit (Abbott Molecular)

No ALK Rearrangement

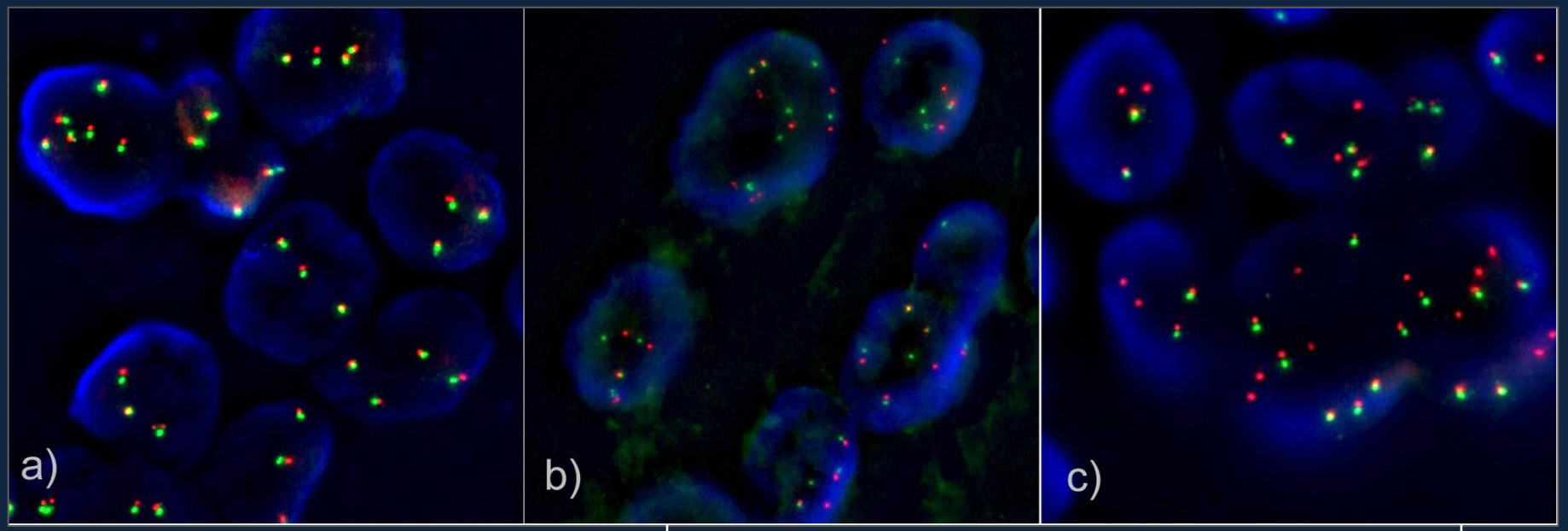
Fused signal

EML4-ALK Fusion

Break apart signal

Single orange signal

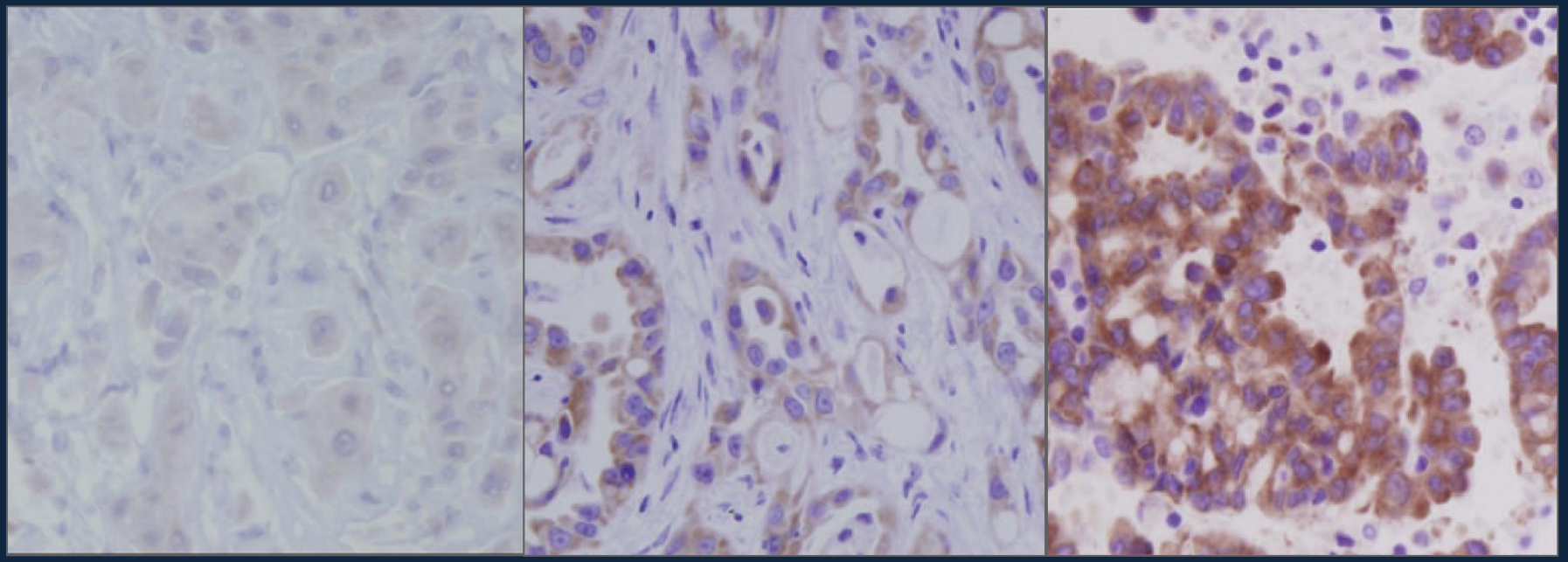
ALK FISH



Courtesy of Pr. L. Bubendorf

ALK IHC

1+ 2+ 3+



Not yet standardized and established!

Kim, J Thorax Oncol 2011

ALK FISH and IHC correlation

The relationship between ALK IHC and FISH in total NSCLC.

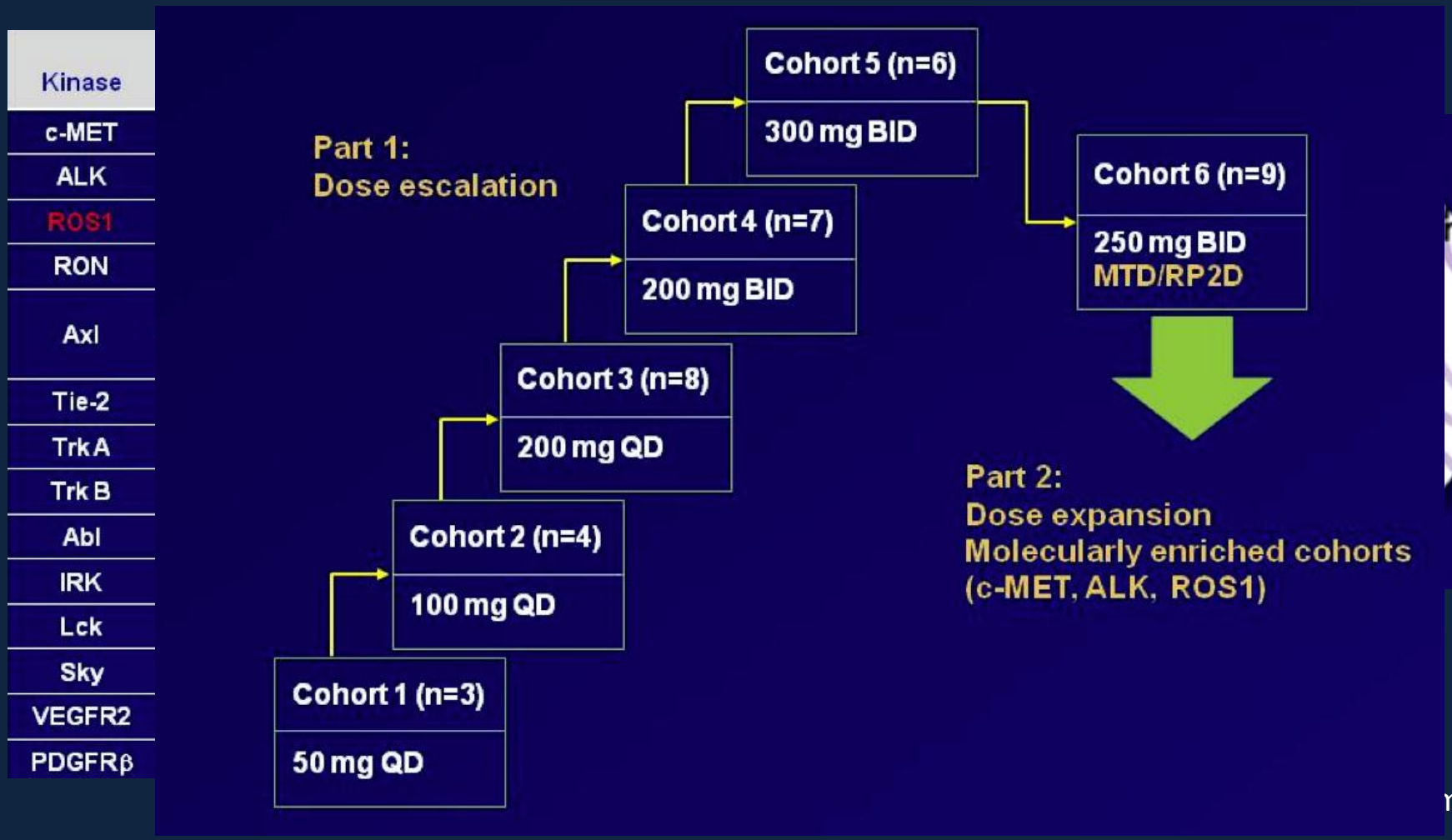
ALK IHC	*ALK* FISH		Total (%)
	(+)	(−)	
0	0 (0)	680 (92.5)	680 (92.5)
1+	0 (0)	20 (2.7)	20 (2.7)
2+	13 (1.8)	7 (1.0)	20 (2.7)
3+	15 (2.0)	0 (0)	15 (2.0)
Total	28 (3.8)	707 (96.2)	735 (100)

IHC, immunohistochemistry; FISH, fluorescence *in situ* hybridization; NSCLC, non-small cell lung cancer.

Paik, Lung Cancer 2011

Targeting ALK (2)

Crizotinib



n 2011

Targeting ALK (3)

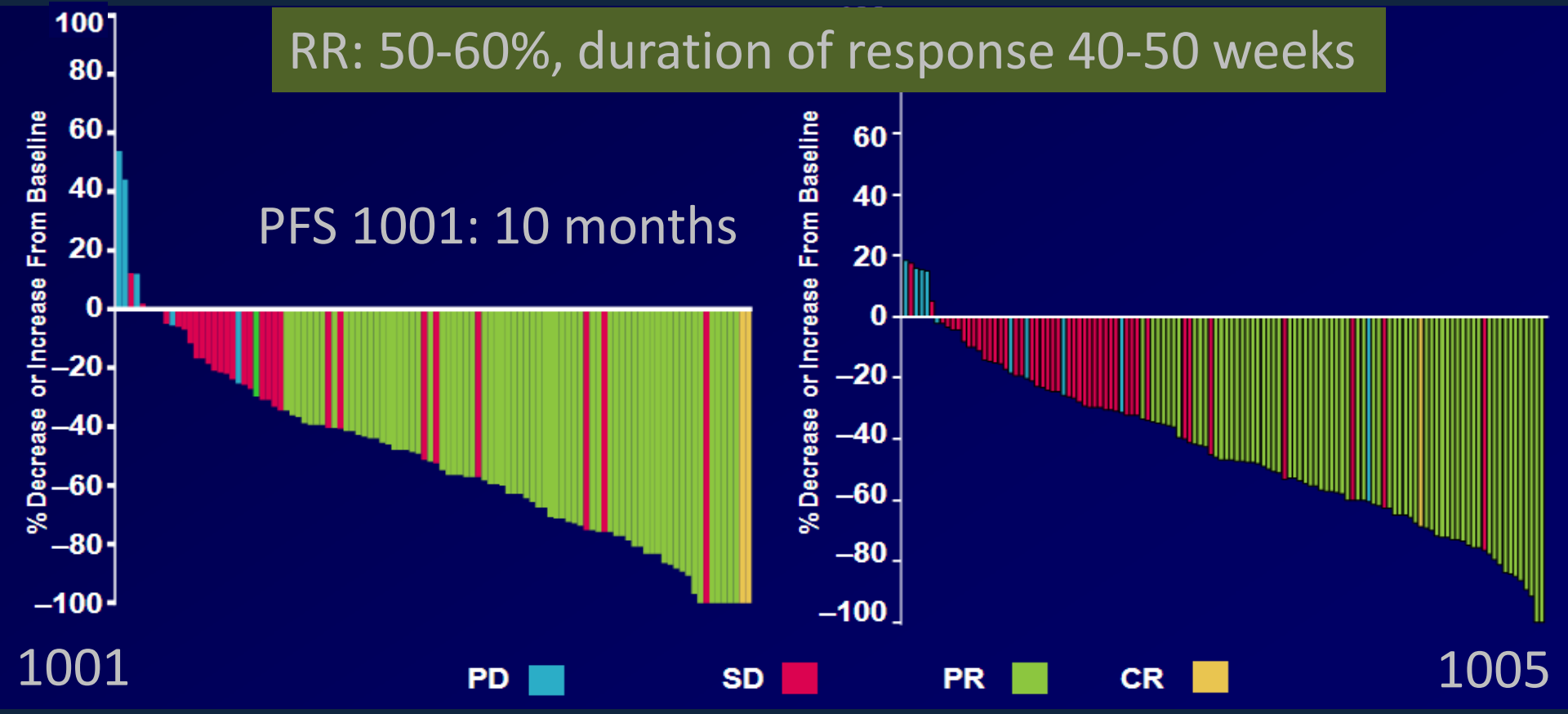
Clinical trials program

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

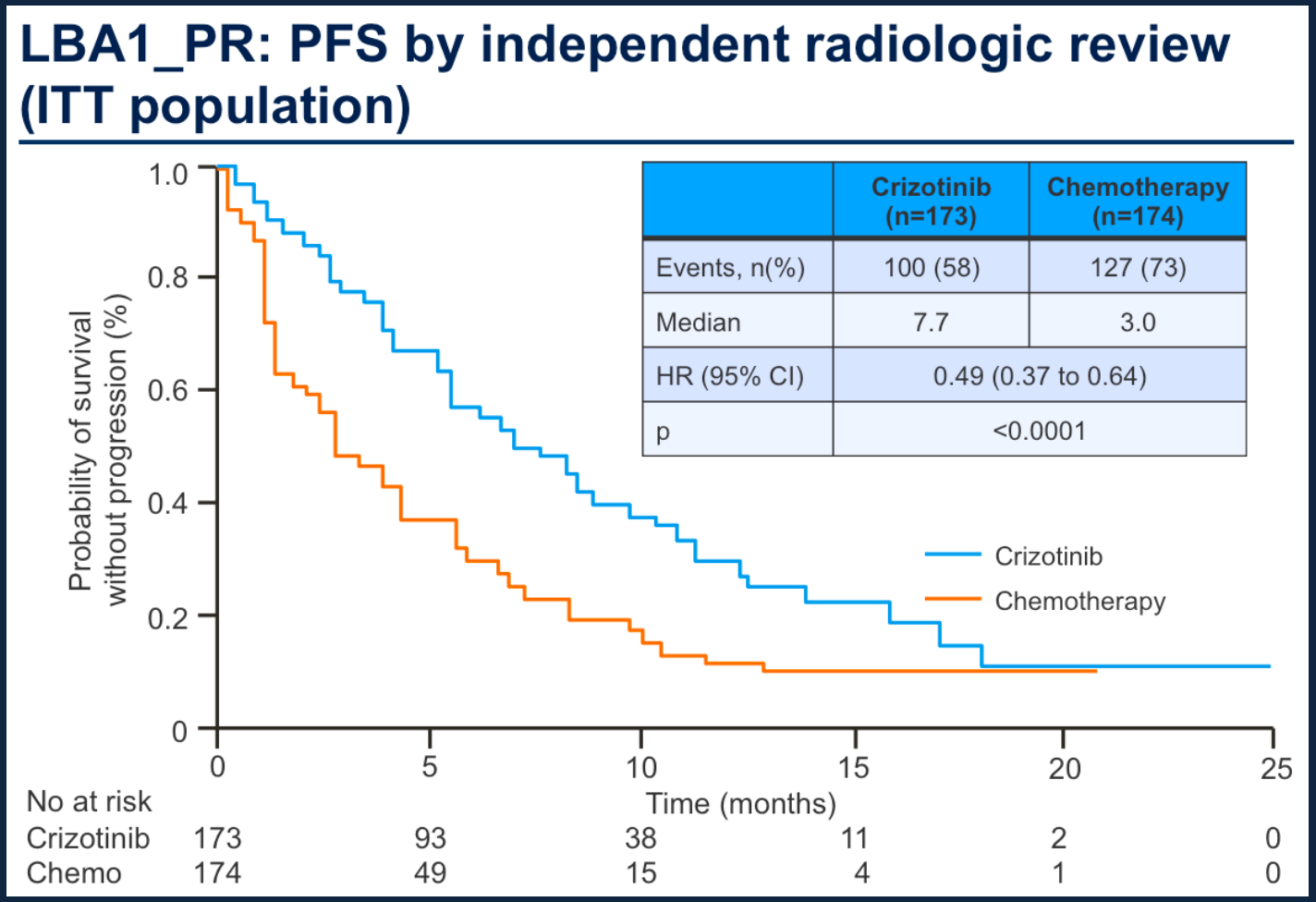
RR: 50-60%, duration of response 40-50 weeks



Camidge, ASCO 2011; Riely, IASLC 2011

Targeting ALK (5)

Profile 1007

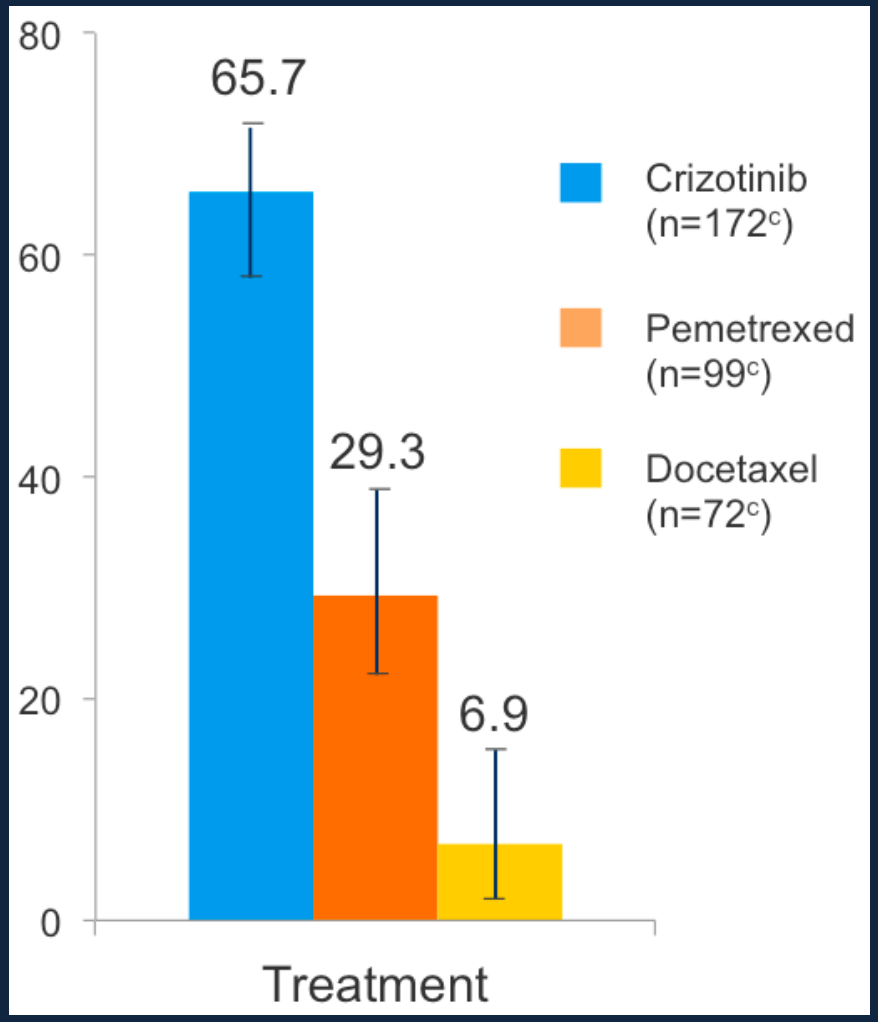


	Crizotinib (n=173)	Chemotherapy (n=174)
Events, n(%)	100 (58)	127 (73)
Median	7.7	3.0
HR (95% CI)	0.49 (0.37 to 0.64)	
p	<0.0001	

Shaw, ESMO 2012

Targeting ALK (6)

Profile 1007

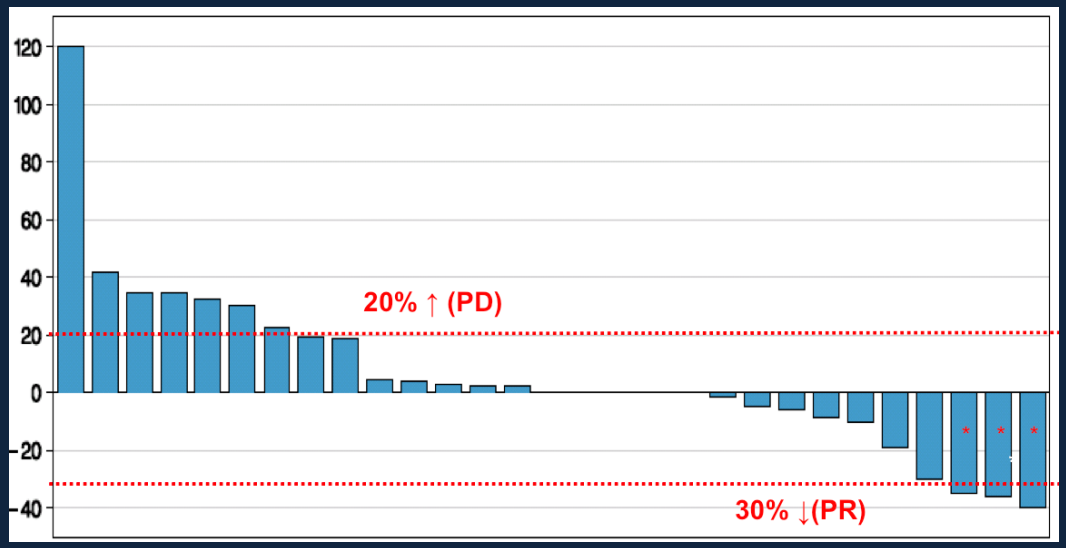


Shaw, ESMO 2012

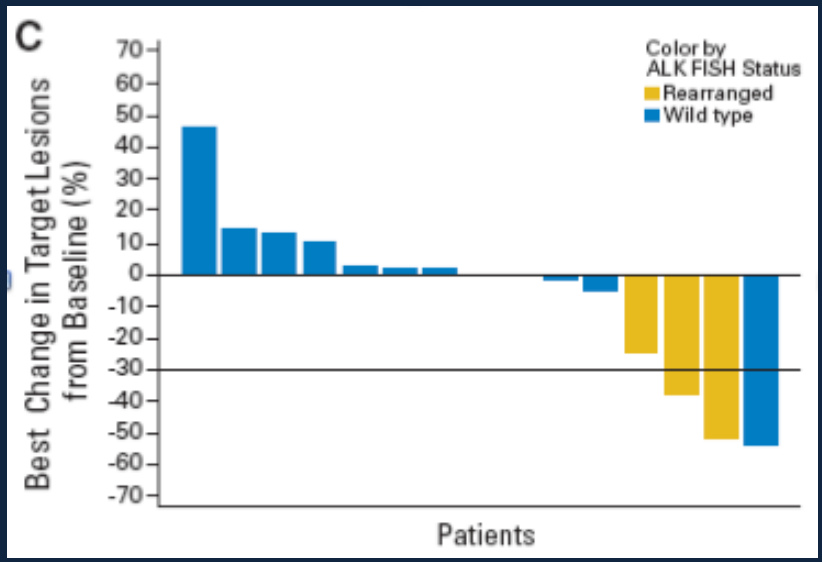
Targeting ALK (7)

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

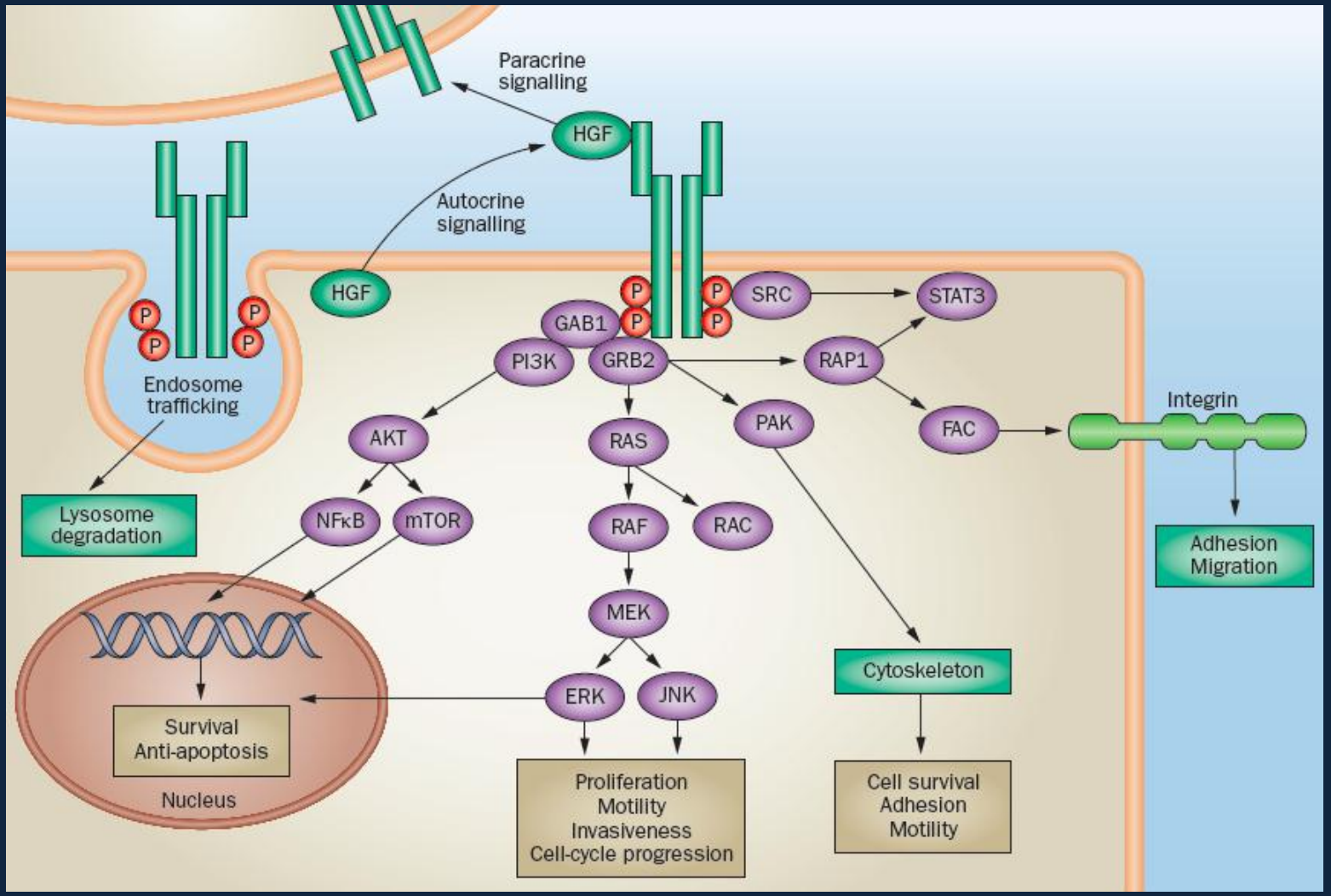
Molecular pathology of NSCLC

More pieces TO THE PUZZLE

3 PIECES OF THIS PUZZLE:

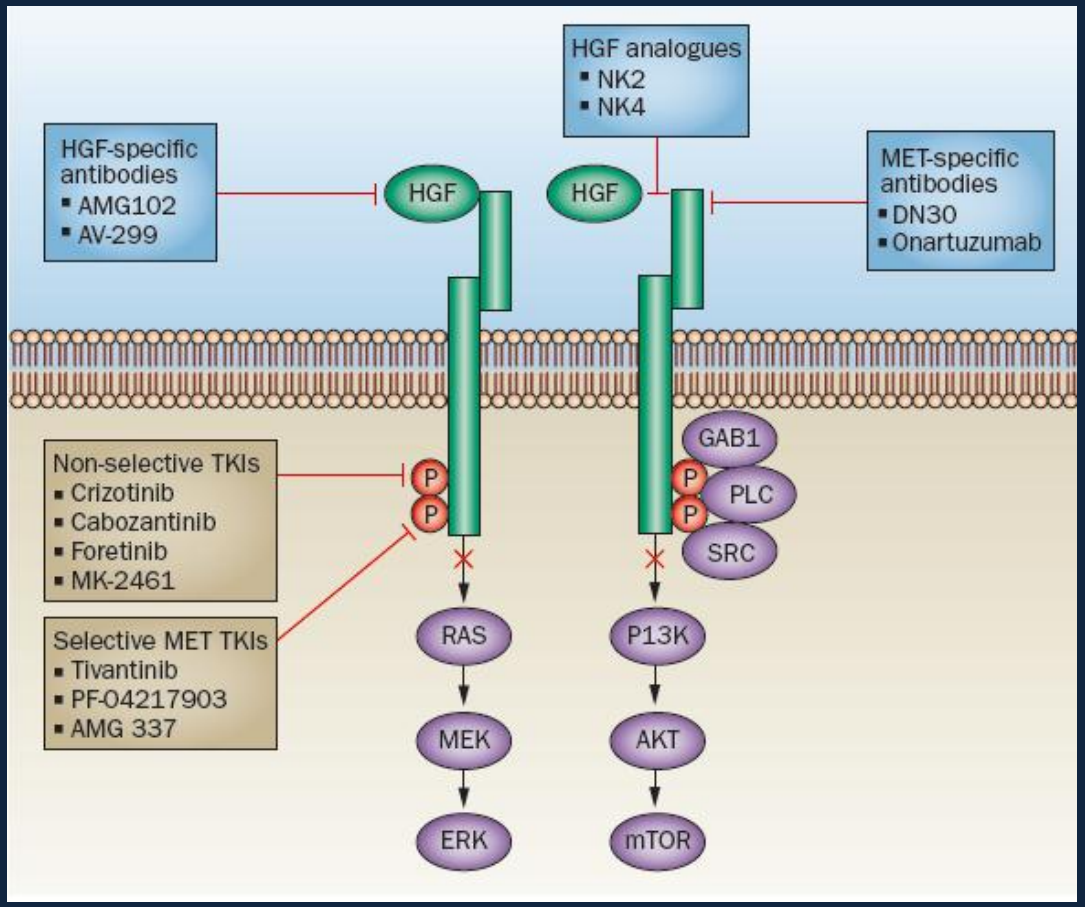
- EGFR: high level of evidence and knowledge
- ALK: growing level of evidence and knowledge
- **MET: Potential future target?**
  - Biomarker variants and clinical relevance: mutation/amplification/overexpression?
  - Biomarker testing method?
  - Clinical demographics and benefit?

Translation in the clinic: targeting MET



Peters & Adjei, NatRev Clin Oncol 2012

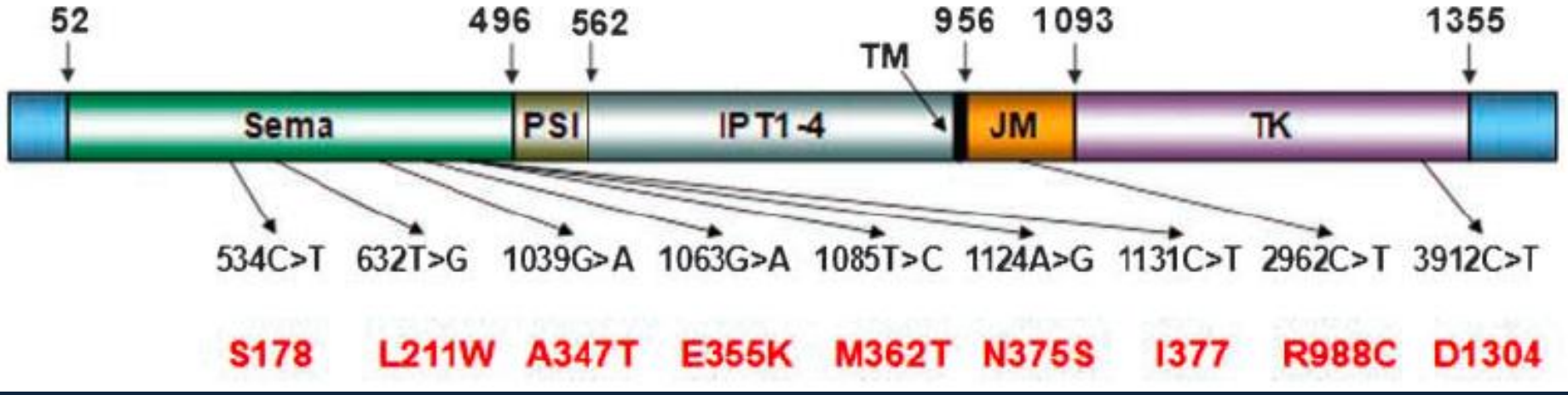
Translation in the clinic: targeting MET



- MET amplification at baseline (0-7% according to technique) and at EGFR TKI resistance (0-22%)
- MET mutations of some unsettled significance (0-25%)
- No dedicated trial data available

Peters & Adjei, NatRev Clin Oncol 2012

MET mutations



Sema, semaphorin domain; PSI, plexins, semaphorins, and integrins domain; IPT1-4, found in immunoglobulin-like regions, plexins, and transcriptional factors; TM, transmembrane region; JM, juxtamembrane domain; TK, catalytic tyrosine kinase domain

Krishnaswamy, CCR 2009

How to evaluate MET role in oncogenesis: IHC?

CONFIRM anti-Total c-MET (SP44) Rabbit Monoclonal Primary Antibody

REF 790-4430

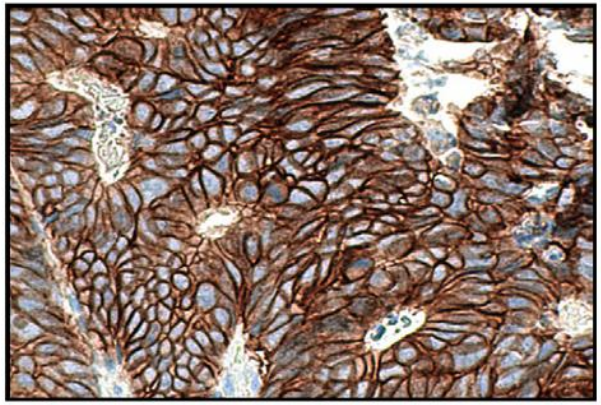
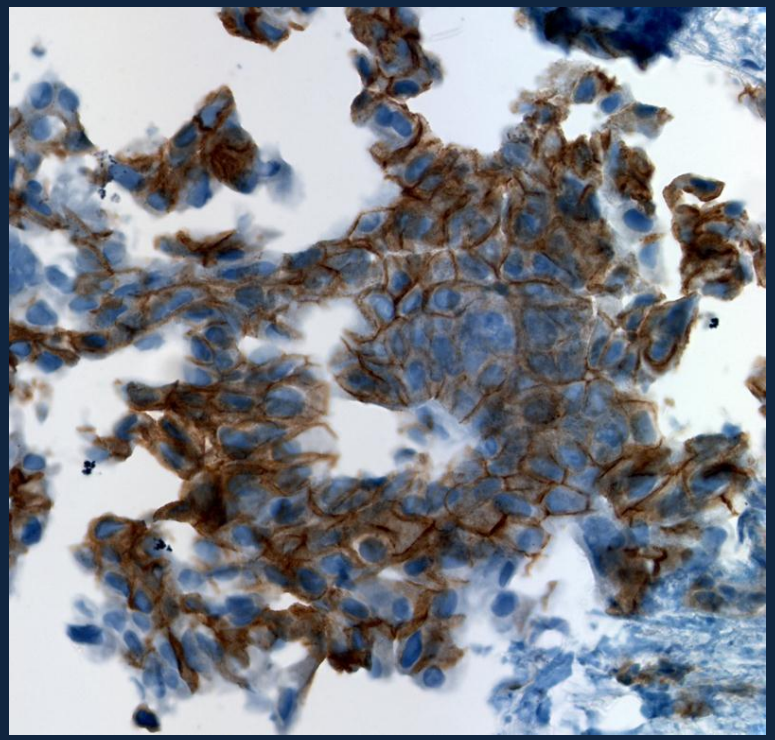


Figure 1. CONFIRM anti-Total c-MET (SP44) Rabbit Monoclonal Primary Antibody cytoplasmic membrane staining of colon carcinoma

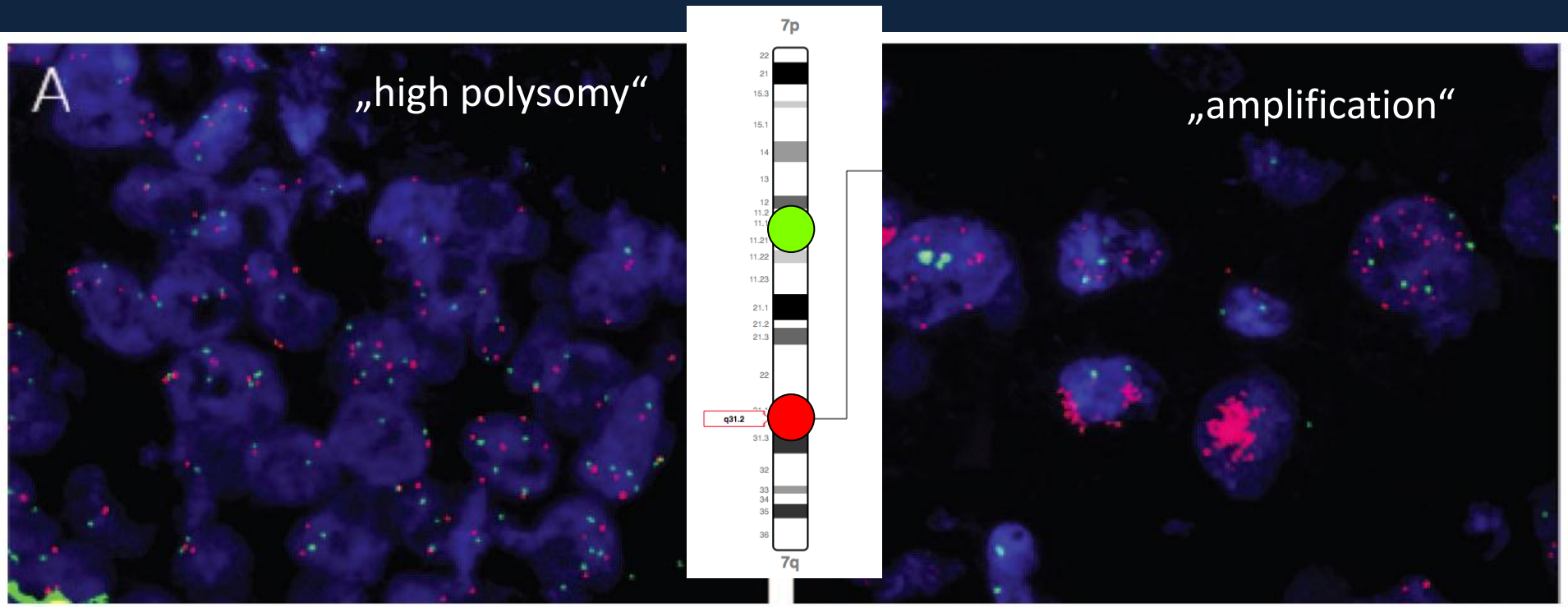
INTENDED USE

Ventana Medical Systems' (Ventana) CONFIRM anti-Total c-MET (SP44) Rabbit Monoclonal Primary Antibody is directed against a membranous and/or cytoplasmic epitope present in human normal epithelial or tumor cells. This antibody may be used to aid in the identification of normal and neoplastic c-MET expressing cells. The antibody is intended for qualitative staining in sections of formalin fixed, paraffin embedded tissue. The

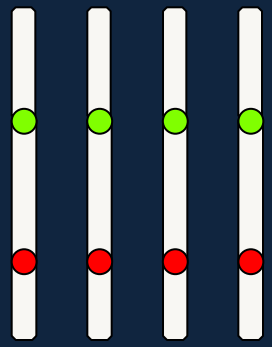


MET ICH: 50% positive
(AC > SqCC)

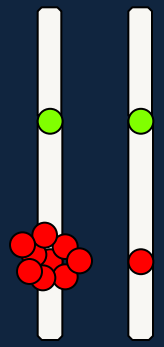
How to evaluate MET role in oncogenesis: FISH?



≥4 signals in ≥40% of cells



MET/CEP7 = ≥2; or clusters



Go H et al; *JTO* 2010

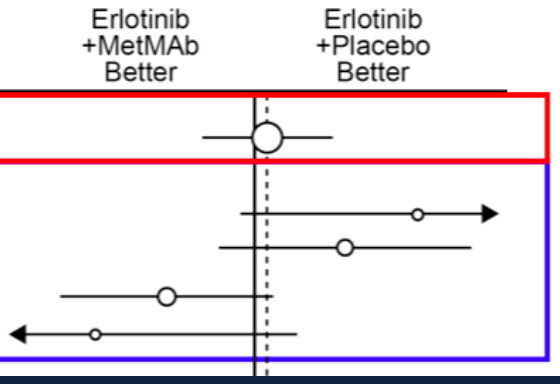
Time for propsective cutomized trials?

		ARQ197/erlotinib		Placebo/erlotinib		
	N	Median PFS (95% CI, months)				Unadjusted HR
Squamous Cell	26/24	3.2	1.9-4.2	2.0	1.8-4.9	HR=1.05
Non-Squamous Cell	58/59	4.4	3.5-7.3	2.3	1.9-3.7	HR=0.71
c-MET FISH >4	19/18	3.6	1.9-5.7	3.6	1.7-3.8	HR=0.71
c-MET FISH >5	8/11	5.6	3.8-NE	3.6	1.8-7.3	HR=0.45

ESMO congress Milan 2010

Anti-Met Monovalent Antibody: PFS Subgroup Analyses in ITT

Baseline Risk Factor	Erlotinib +Placebo Median (wk)	Erlotinib +MetMAb Median (wk)	Hazard Ratio	(95% CI)	p-Value
All Subjects (n=128)	11.1	9.6	1.09	(0.71–1.67)	0.699
Met IHC					
0 (n=18)	8.8	5.9	2.94	(0.92–9.40)	0.058
1 (n=38)	11.4	6.1	1.82	(0.79–4.18)	0.151
2 (n=51)	6.4	12.9	0.57	(0.28–1.14)	0.105
3 (n=14)	6.3	11.6	0.36	(0.09–1.33)	0.108



Schiller, ASCO 2010; Spigel, ESMO 2010

Conclusions: Customized treatment for lung cancer

- The majority of lung adenocarcinoma in Caucasian patients harbor potentially “drugable” genetic oncogenic alteration
- A similar picture, with some more complexity, is emerging on lung squamous cell carcinoma
- Further progress mandates a move from unselected NSCLC trial designs to molecularly-driven clinical trials

Two main challenges

How to use the enormous ad growing amount of biological data for our patients' benefit – in a fast and efficient manner?

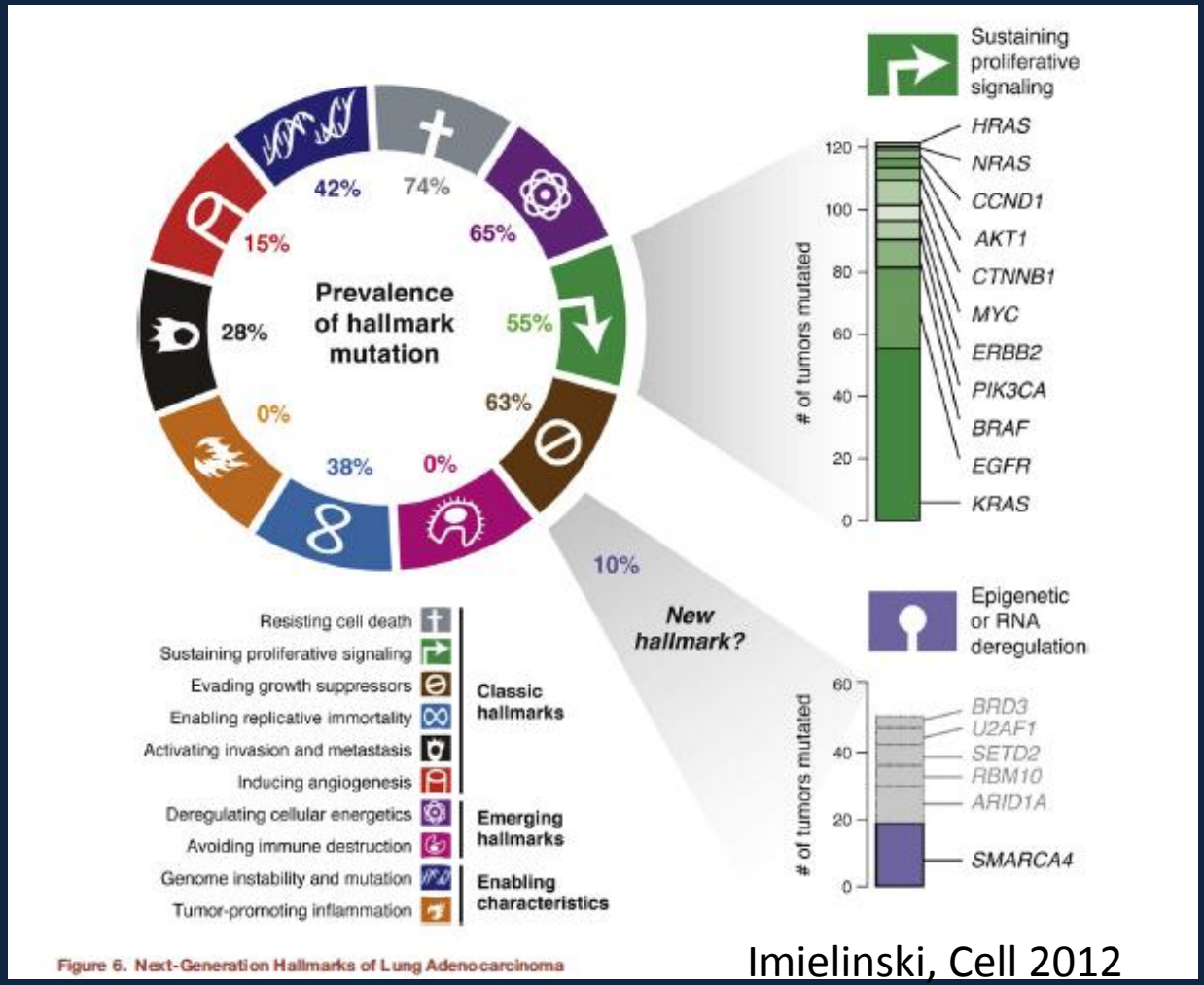


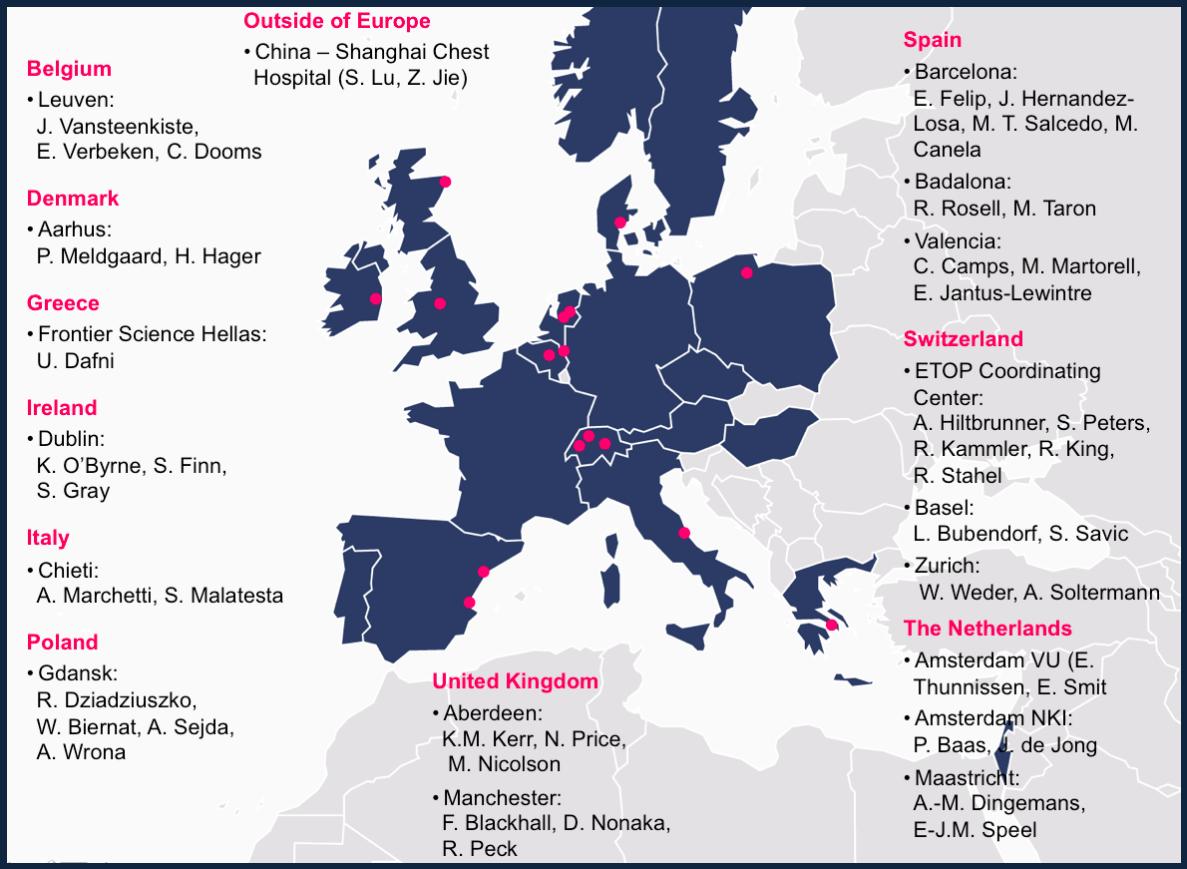
Figure 6. Next-Generation Hallmarks of Lung Adenocarcinoma

Imielinski, Cell 2012

Two main challenges

How to improve network collaborations in order to:

- Perform prospective evidence-generating trials for very rare subsets of patients?
- Allow early access to new drugs to more patients



Thanks for your attention